EXHIBIT A - PART 3 OF 7

EXHIBIT 4

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Pomalidomide (CC4047) Plus Low-Dose Dexamethasone As Therapy for Relapsed Multiple Myeloma

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ABSTRACT

Purpose
Thalidomide and lenalidomide are immunomodulatory drugs (IMiDs) that produce high remission rates in the treatment of multiple myeloma. Pomalidomide is a new IMiD with high in vitro potency. We report, to our knowledge, the first phase II trial of pomalidomide administered in combination with low-dose dexamethasone for the treatment of relapsed or refractory multiple myeloma.

Patients and Methods
Pomalidomide was administered orally at a dose of 2 mg daily on days 1 through 28 of a 28-day cycle. Dexamethasone 40 mg daily was administered orally on days 1, 8, 15, and 22 of each cycle. Responses were recorded using the criteria of the International Myeloma Working Group.

Results
Sixty patients were enrolled. Thirty-eight patients (63%) achieved confirmed response including complete response in three patients (5%), very good partial response in 17 patients (28%), and partial response in 18 patients (30%). Responses were seen in 40% of lenalidomide-refractory patients, 37% of thalidomide-refractory patients, and 60% of bortezomib-refractory patients. Responses were seen in 74% of patients with high-risk cytogenetic or molecular markers. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity consisted of anemia (5%), thrombocytopenia (3%), and neutropenia (32%). One patient (1.6%) had a thromboembolic event. The median progression-free survival time was 11.6 months and was not significantly different in patients with high-risk disease compared with patients with standard-risk disease.

Conclusion
The combination of pomalidomide and low-dose dexamethasone is extremely active in the treatment of relapsed multiple myeloma, including high response rates in patients refractory to other novel agents.

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INTRODUCTION

Since the introduction of novel agents into clinical practice, median survival in multiple myeloma has improved by 50%.[1] The introduction of thalidomide represented a major milestone in the treatment of multiple myeloma. Thalidomide was initially used for treatment of multiple myeloma because of its antiangiogenic properties.[2] Promising clinical results led to the development of a class of thalidomide analogs termed immunomodulatory drugs (IMiDs). In relapsed myeloma, thalidomide alone has response rates of 30% to 35%.[2,3] The addition of dexamethasone to thalidomide improves responses to 40% to 50%.[4] Lenalidomide and dexamethasone combination has achieved response rates of 55% to 60%[5,6] in relapsed myeloma and 90% in newly diagnosed myeloma.[7,8] Bortezomib alone has a response rate of 38% in patients who have experienced relapse.[9] The addition of other chemotherapy drugs, such as pegylated doxorubicin, cyclophosphamide,[10-13] or multiple drugs,[14] to bortezomib improves response rates to 55% to 82%. Despite these improvements, curative therapy does not exist, and all patients eventually experience relapse. New agents for the treatment of relapsed myeloma are still needed.

Pomalidomide (CC4047) is a new IMiD with high in vitro potency. Clinical studies are ongoing. IMiDs are hypothesized to act through multiple mechanisms. Evidence suggests that in addition

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to antiangiogenic effects,[15] IMiDs may have antineoplastic effects by blocking signaling through nuclear factor-κB[16] and may induce apoptosis via the caspase-8/death receptor pathway.[17] IMiDs have potent immunomodulatory properties including downregulating tumor necrosis factor[18,19] and interleukin-1β,[20] augmentation of anti-myeloma natural killer cell activity,[21,22] and stimulation of cytotoxic T cells.[23,24] Data suggest that pomalidomide is the most potent of the IMiDs.[25-28] Phase I trials established pomalidomide as well tolerated in doses ranging from 1 to 5 mg/d.[29,30] We report on the first phase II trial of pomalidomide combined with low-dose dexamethasone in patients with relapsed or refractory multiple myeloma.

Patients and Methods

Eligibility

Patients were eligible to enter onto the study if they had relapsed or refractory multiple myeloma. They had to have at least one but no more than three prior regimens. Induction therapy followed by autologous stem-cell transplantation (ASCT) and consolidation was considered one regimen. Patients were required to have measurable disease defined by one of the following: serum monoclonal protein greater than 10 g/L, serum immunoglobulin free light chain (FLC) more than 10 mg/dL and an abnormal FLC ratio, urine light-chain excretion $\geq$ 200 mg/24 h, measurable soft tissue plasmacytoma that had not been radiated, or greater than 30% plasma cells in bone marrow. Patients also were required to have platelet count greater than 75×10^9/L, absolute neutrophil count greater than 1.0×10^9/L, and creatinine less than 221 μmol/L (2.5 mg/dL). All previous cancer therapy, including chemotherapy and investigational agent, must have been discontinued $\geq$ 2 weeks before study registration. The following patients were excluded: patients with uncontrolled infection, another active malignancy, deep vein thrombosis that had not been therapeutically anticoagulated, Eastern Cooperative Oncology Group performance status of 3 or 4, or grade 3 or 4 peripheral neuropathy; pregnant or nursing women; women of child-bearing potential who were unwilling to use a dual method of contraception; and men who were unwilling to use a condom. The study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki. This trial is registered at ClinicalTrials.gov (No. NCT00558896).

Treatment Schedule

Pomalidomide was administered orally at a dose of 2 mg daily on days 1 through 28 of a 28-day cycle. Dexamethasone was administered orally at a dose of 40 mg daily on days 1, 8, 15, and 22 of each cycle. Patients also received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full-dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Granulocyte colony-stimulating factor was not allowed to avoid dose reductions but could be used if a patient developed neutropenic fever.

Dose adjustments were permitted based on toxicity as described in the next section. Pomalidomide was to be permanently discontinued in the event of grade 4 rash, neuropathy, or hypersensitivity or grade 3 or higher bradycardia or cardiac arrhythmia. Pomalidomide was progressively reduced for other related grade 3 or higher adverse events to a dose level of 2 mg for 21 days each 28-day cycle. Subsequent dose reductions were performed in 0.5-mg increments for 21 days each 28-day cycle. When grade 3 or 4 adverse events occurred before day 15 of a cycle and resolved to grade 2 or lower before day 28 of the cycle, pomalidomide was resumed at the next lower dose level, with the next cycle continuing at the reduced dose level. For grade 3 or 4 adverse events occurring on or after day 15 of a given cycle, pomalidomide was held for the remainder of the cycle and reduced by one dose level beginning with the next cycle. Dose reductions were permitted for dexamethasone-related toxicity and involved lowering the dose of dexamethasone progressively to 20, 12, 8, and 4 mg once weekly. Patients unable to tolerate the lowest doses of pomalidomide or dexamethasone had to stop therapy with that agent permanently.

Response and Toxicity Criteria

Responses were assessed according to published criteria of the International Myeloma Working Group.[31] A partial response (PR) was defined as $\geq$ 50% reduction in the level of the serum monoclonal protein and/or a reduction in 24-hour urinary light-chain excretion by $\geq$ 90% or to less than 200 mg. On study, if the bone marrow was the only measurable parameter, $\geq$ 50% reduction in bone marrow plasma cells was required in place of monoclonal protein, provided the baseline percentage was $\geq$ 30%. In addition to these criteria, if a plasmacytoma was present at baseline, $\geq$ 50% reduction in the size of soft tissue plasmacytomas was also required.

Complete response (CR) required complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and less than 5% plasma cells on bone marrow examination. Stringent CR required CR as just defined plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. A very good PR (VGPR) required, in addition to criteria for PR, serum and urine monoclonal protein detectable only on immunofixation but not on electrophoresis or $\geq$ 90% reduction in serum monoclonal protein and 24-hour urine monoclonal protein less than 100 mg/24 h. In patients in whom the only measurable disease was by serum FLC levels, CR required a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed earlier. VGPR in such patients was defined as a more than 90% decrease in the difference between involved and uninvolved FLC levels. All response categories (CR, stringent CR, VGPR, and PR) require two consecutive assessments made at any time before the institution of any new therapy.

Disease progression required any one of the following criteria: increase in serum monoclonal protein of 25% or higher above the lowest response level and an absolute increase by more than 5 g/L; increase in urine monoclonal protein by 25% above the lowest remission value and an absolute increase in excretion by $\geq$ 200 mg/24 h; increase in size of soft tissue plasmacytoma by more than 50% or appearance of a new plasmacytoma; definite appearance of bone lesions or increase in the size of existing bone lesions by more than 50%; or unexplained hypercalcemia of more than 2.875 mmol/L (> 11.5 g/dL). The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) was used to grade adverse events and to assign perceived attribution of these events to the study treatment regimen.

We were interested in specifically looking at responses among patients refractory to other novel agents, including other IMiDs, and high-risk patients. For this purpose, refractory was defined, according to recently published guidelines,[31] as failing to respond or disease progression during treatment or within 60 days of treatment completion. High risk was defined, according published criteria,[31] as cytogenetic studies showing hypodiploidy or karyotypic deletion of chromosome 13, fluorescent in situ hybridization showing presence of translocations t(4;14) or t(14;16) or deletion 17p, or plasma cell labeling index $\geq$ 3%.

Statistical Design and Analysis

The primary end point was the proportion of confirmed responses (CR, VGPR, or PR). The study used a single-stage Simon design with an interim analysis to test that the true confirmed response rate was at most 20% versus the alternative that it was at least 45%, with a significance level of $P = .05$ and 90% power. The regimen would be declared ineffective if a maximum of 10 confirmed responses were observed in the first 34 evaluable patients. A second cohort of patients was added to test whether increasing the dose from 2 to 4 mg/d in nonresponders was effective (ie, if the true confirmed response rate was at most 5% v the alternative that it was at least 30%). This single-stage Simon design required 14 patients at the higher dose and had a power of 95% with a significance level of $P = .15$. On the basis of data from the first cohort, it was anticipated that 23 patients were required to accrue 14 patients that would be eligible for dose escalation (not responding to therapy within two cycles and absence of grade $\geq$ 3 adverse events). The regimen would be declared ineffective in this subgroup if at most one confirmed response was observed in the first 14 evaluable patients. Secondary end points included overall survival (OS), progression-free survival (PFS), duration of response (DOR), and adverse event profile.

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All analysis is based on the intent-to-treat principle. Data are summarized both overall and within each cohort, where appropriate. Exact binomial CIs are constructed for the primary end point of confirmed response. A graphical representation of the antitumor activity (ie, percent change from baseline to 12 weeks in the measurable disease parameter, as defined earlier) was performed using the waterfall plot. The distributions of OS time (time from study entry to death), PFS time (time from study entry to disease progression or death), and DOR (time from first documentation of response until progression or death) are estimated using the Kaplan-Meier method. Simple descriptive statistics are used to summarize the adverse event profile and baseline characteristics.

Results

Patient Population

Overall, 60 patients (37 in the first cohort; 23 in the second cohort) were accrued to the study from November 2007 through August 2008. All patients were evaluable. Patient demographics and clinical characteristics at study entry are listed in Table 1. The median age was 66 years (range, 35 to 88 years). Twenty-eight percent, 37%, and 35% of patients had one, two, and three prior regimens, respectively. Previous ASCT was performed in 65% of patients, including nine who had two previous ASCTs. Sixty-two percent of patients had previous IMiD therapy, including 21 patients with prior lenalidomide and 28 patients with prior thalidomide. Twenty patients had prior bortezomib. Baseline peripheral neuropathy was present in 27 patients (45%). The median time from diagnosis to enrollment onto study was 44 months. Nineteen patients (32%) were classified as high risk.

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 60)	%
Time from diagnosis to on study, months		
Median	44	
Range	9.1-192.5	
Age, years		
Median	65.5	
Range	35-88	
Male	36	60
ISS stage		
I	12	28
II	17	40
III	14	32
β_2-microglobulin, μg/mL		
Median	3.5	
Range	1.5-14.0	
PCLI, %		
Median	0.7	
Range	0.0-9.6	
PCLI ≥ 3%	8	13
Baseline neuropathy		
Grade 1	24	40
Grade 2	3	5
Cytogenetic studies available	57	95
Normal	38	67
Abnormal	19	33
Deletion 13	4	
Complex abnormalities	12	
Other	3	
FISH studies available	30	50
High risk*	9	30
Prior Treatment		
No. of prior chemotherapy regimens		
1	17	28
2	22	37
3	21	35
Transplantation	39	65
Previous IMiD use	37	62
Previous lenalidomide	21	35
Previous thalidomide	28	47
Previous bortezomib	20	33

Abbreviations: ISS, International Staging System; PCLI, plasma cell labeling index; FISH, fluorescent in situ hybridization; IMiD, immunomodulatory drugs.
*High-risk FISH was defined as deletion 17 or 17p, t(4;14), or t(14;16).

Follow-Up

The median number of cycles administered was seven (range, one to 14 cycles). Thirty-three patients continue to receive treatment. The major cause for stopping study drug was disease progression (n = 20). Five patients withdrew as a result of physician or patient discretion. Two patients died on study. One patient, an 88-year-old female, died 3.3 months after initiating study treatment as a result of valvular heart disease not related to study treatment. The second patient, an 82-year-old female, developed neutropenic fever and pneumonia during cycle 1. Her death from infection was attributed to her treatment. Two additional patients died from disease progression after discontinuing the study drug. The median follow-up time in the remaining living patients is 7.4 months (range, 0.9 to 13 months).

Efficacy

Twenty-one (62%; 95% CI, 44% to 78%) of the first 34 patients met the protocol-defined criteria for confirmed response, thus passing the threshold for success. In the second cohort, only four patients were escalated to the higher dose of 4 mg/d, of whom one patient had a confirmed VGPR. Overall, 38 (63%; 95% CI, 50% to 75%) of 60 patients had confirmed responses (CR: n = 3, 5%; VGPR: n = 17, 28%; and PR: n = 18, 30%). Figure 1 shows the waterfall plot for the 49 patients who were on study at 12 weeks, with approximately 82% of patients demonstrating a ≥ 25% decrease in their measurable parameter from baseline to 12 weeks.

Twenty, 16, and 10 patients were considered refractory to lenalidomide, thalidomide, and bortezomib, respectively; of these patients, confirmed responses were seen in eight (40%), six (37%), and six (60%) patients, respectively. Additionally, five patients were refractory to both bortezomib and lenalidomide, of whom two patients had a confirmed PR and one had a confirmed VGPR. Of the 19 patients who were considered high risk, 14 patients (74%; 95% CI, 49% to 91%) had confirmed responses including one CR and five VGPRs (Table 2).

The median DOR has not been achieved yet; 97% of patients continued to respond 6 months after first documentation of response. The median OS time has not been achieved yet; 94% of patients were alive at 6 months. The median PFS time was 11.6 months (95% CI, 9.2 months to not reached). PFS was not significantly different in patients with high-risk disease compared with patients with standard-risk disease (Fig 2).

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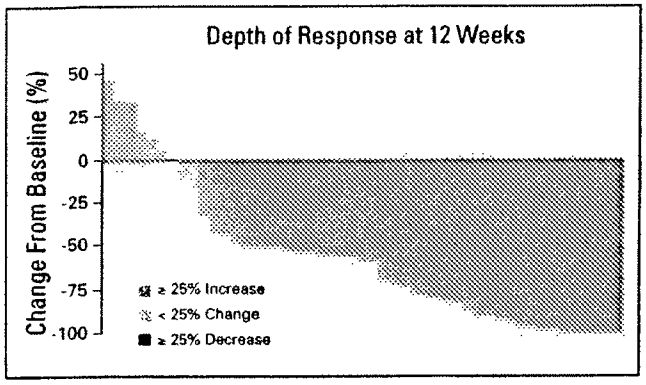

Fig 1. Each bar represents the percent change in the measurable parameter, whether serum, urine, or bone marrow as a percent change from baseline at 12 weeks.

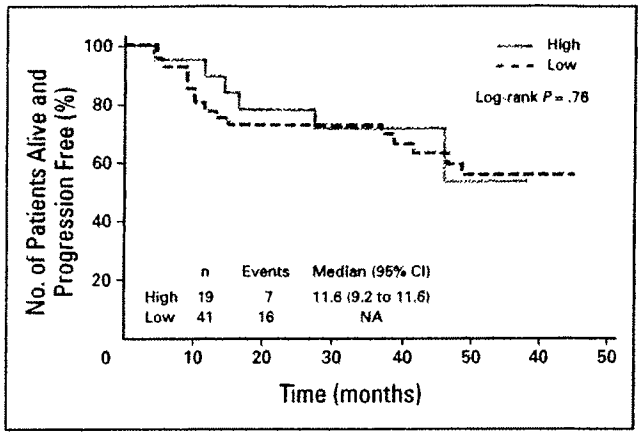

Fig 2. Progression-free survival based on presence or absence of high-risk features.

Toxicity

Toxicity was defined as an adverse event considered possibly, probably, or definitely related to treatment. Treatment was well tolerated. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia (5%), thrombocytopenia (3%), and neutropenia (32%). Among patients who developed grade 3 or 4 neutropenia, all of the patients first experienced the neutropenia in cycles 1 to 3. No new patients experienced grade 3 or 4 neutropenia in cycle 4 or later.

The most common grade 3 or 4 nonhematologic toxicities consisted of fatigue (17%) and pneumonia (8%). Other grade 3 or 4 nonhematologic toxicities seen in less than 5% of patients included diarrhea, constipation, hyperglycemia, and neuropathy. A total of 24 patients (40%) experienced neuropathy during treatment (grade 1, n = 18; grade 2, n = 5; and grade 3, n = 1); 14 of the 24 patients had neuropathy at baseline, of whom four patients had a worsening of neuropathy grade during treatment. Among the 33 patients without neuropathy at baseline, 30% reported neuropathy during treatment (all grade 1). Patients received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full-dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Forty-five patients took aspirin, and 15 patients were anticoagulated, one with heparin and 14 with warfarin. One patient (1.6%) had a thromboembolic event. Toxicities are listed in Table 3.

DISCUSSION

This study shows the impressive activity of pomalidomide in relapsed refractory myeloma. The most striking feature of our trial is the response seen in patients who have been shown to be refractory to other novel agents including lenalidomide, thalidomide, and bortezomib. Patients with myeloma who have experienced progression after multiple novel agents have limited treatment options. The 40% response rate in lenalidomide-refractory patients implies non–cross resistance

Table 2. Confirmed Responses in Refractory and High-Risk Patients

Response	Total No. of Patients	CR* No.	CR* %	VGPR No.	VGPR %	PR No.	PR %	SD No.	SD %	PD No.	PD %	NA No.	NA %	RR† No.	RR† %
Confirmed responses in refractory patients															
Confirmed response	60	3	5	17	28	18	30	15	25	6	10	1	2	38	63
Bortezomib refractory	10	1	10	2	20	3	30	4	40	0	0	0	0	6	60
Lenalidomide refractory	20	0	0	1	5	7	35	9	45	3	15	0	0	8	40
Thalidomide refractory	16	0	0	2	12.5	4	25	6	37.5	4	25	0	0	6	37.5
Bortezomib and lenalidomide refractory	5	0	0	1	20	2	40	2	40	0	0	0	0	3	60
Confirmed responses in high-risk patients															
High risk‡	19§	1	5	5	27	8	42	4	21	1	5			14	74
Deletion 13	4	0	0	1	25	3	75	0	0	0	0			4	100
t(4;14)	1	0	0	0	0	0	0	1	100	0	0			0	0
t(14;16)	3	0	0	0	0	2	67	1	33	0	0			2	67
17p–	5	0	0	3	60	2	40	0	0	0	0			5	100
PCLI ≥ 3%	8	1	12.5	2	25	2	25	2	25	1	12.5			5	63

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessed for disease; RR, response rate; PCLI, plasma cell labeling index.
*Among the CRs, there were two CRs and one stringent CR.
†RR = CR + VGPR + PR.
‡High risk was defined as PCLI ≥ 3%; deletion 17p, t(4;14), or t(14;16) by fluorescent in situ hybridization; or deletion 13 by conventional cytogenetics.
§Two patients had two high-risk factors.

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Table 3. Maximum Severity of Toxicities

Toxicity	No. of Patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology					
Anemia	29	17	3	0	0
Lymphopenia	0	1	3	0	0
Neutropenia	5	11	15	4	0
Thrombocytopenia	13	4	2	0	0
Leukopenia	9	14	8	2	0
Constitutional symptoms					
Fatigue	17	17	10	0	0
GI					
Anorexia	5	0	0	0	0
Vomiting	4	0	0	0	0
Nausea	8	1	0	0	0
Diarrhea	7	4	1	0	0
Constipation	0	8	3	0	0
Infection/febrile neutropenia					
Pneumonia	0	1	3	1	1
Metabolic/laboratory					
Hyperglycemia	0	7	3	0	0
Neurology					
Confusion	0	5	0	0	0
Insomnia	0	7	0	0	0
Agitation	0	7	0	0	0
Peripheral neuropathy	17	5	1	0	0
Cardiovascular					
Thrombosis	0	0	1	0	0

NOTE. Toxicities have an attribution of possibly, probably, or definitely related to study drugs. National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) was used to grade adverse events.

for this agent, suggesting a special niche for this drug in the treatment of patients who have experienced relapsed. Also notable is the high remission rate (74%) in patients with high-risk disease, a group of patients who are particularly resistant to treatment at the time of relapse. Short duration of remission is generally a problem in patients with high-risk disease. Although follow-up is short in our cohort, preliminary data suggest that the PFS is the same regardless of the presence or absence of high-risk features.

These results are impressive considering that response rates rival those seen with lenalidomide despite using only one third of the dose of concomitant dexamethasone. Lenalidomide was approved by the US Food and Drug Administration and the European Medicines Agency based on the results of two randomized phase III trials that showed that the combination of lenalidomide and high-dose dexamethasone was superior to high-dose dexamethasone alone.[5,6] Much of the toxicity of the lenalidomide plus high-dose dexamethasone regimen was a result of the high-dose dexamethasone. Preliminary results from an Eastern Cooperative Oncology Group randomized study presented in abstract form show that lenalidomide with weekly low-dose dexamethasone, despite lower response rates, is safer and associated with improved survival in patients with newly diagnosed multiple myeloma compared with lenalidomide plus high-dose dexamethasone.[32] The choice to use low-dose weekly dexamethasone in our trial was based on these results, which may account for the low rate of thromboembolic events seen in this trial. A phase I trial including 24 patients used single-agent pomalidomide and found that 54% of patients experienced a PR or better, including four patients (17%) with CR.[29] On the basis of these data, it is not clear how much value dexamethasone adds to this combination. These results also compare well with studies using other novel agents and combinations in this patient population (Table 4).

Toxicity in this trial was mild and consisted primarily of neutropenia. Neutropenia was seen mainly in the first three cycles, a fact that suggests that the etiology of the myelosuppression is multifactorial, reflecting the activity of the underlying myeloma as well as the toxicity of the regimen. Comparing across trials is also complicated because granulocyte colony-stimulating factor was not allowed in our trial but has been used in many of the comparable trials.

We conclude that the combination of pomalidomide and low-dose dexamethasone is highly active and well tolerated in the treatment of relapsed/refractory multiple myeloma. While waiting for the data to mature for the survival end points, we plan to investigate the effect of pomalidomide and low-dose dexamethasone in phase II trials for lenalidomide- and bortezomib-refractory patients to better define response rates in these populations. Data from this phase II study

Table 4. Novel Agents for the Treatment of Relapsed Multiple Myeloma

Study	Regimen	Dexamethasone Dose per Cycle (mg)	% of Patients		
			DVT	CR + VGPR	≥ PR
Dimopoulos et al[33]	Thal/dex	480	7	—	55
Anagnostopoulos et al[34]	Thal/dex	480	8	—	47
Weber et al[6]	Len/dex	480	14	24	61
Dimopoulos et al[5]	Len/dex	480	11	24	60
Orlowski et al[13]	Bortez; Bortez/PLD	—	1; 1	19; 27	41; 44
Palumbo et al[14]	VMPT	—	0	43	67
Reece et al[10]	Bortez/cyclo/pred	—	—	32	70
Davies et al[11]	Bortez/cyclo/dex	320	NR	31	75
Kropff et al[12]	Bortez/cyclo/dex	160	0	16	82
Current study	Pom/dex	160	2	33	63

Abbreviations: DVT, deep vein thrombosis; CR, complete response; VGPR, very good partial response; PR, partial response; Thal/dex, thalidomide and dexamethasone; Len/dex, lenalidomide and dexamethasone; Bortez, bortezomib; Bortez/PLD, bortezomib and pegylated liposomal doxorubicin; VMPT, bortezomib, melphalan, prednisone, and thalidomide; Bortez/cyclo/pred, bortezomib, cyclophosphamide, and prednisone; Bortez/cyclo/dex, bortezomib, cyclophosphamide, and dexamethasone; NR, not reported; Pom/dex, pomalidomide and dexamethasone.

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justifies further exploration of using pomalidomide in combination with other novel agents.

[illegible] of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Data analysis and interpretation: Martha Q. Lacy, Suzanne R. Hayman, Morie A. Gertz, Angela Dispenzieri, Francis Buadi, Shaji Kumar, Philip R. Greipp, John A. Lust, Stephen J. Russell, David Dingli, Robert A. Kyle, Rafael Fonseca, P. Leif Bergsagel, Vivek Roy, Joseph R. Mikhael, A. Keith Stewart, Kristina Laumann, Jacob B. Allred, Sumithra J. Mandrekar, S. Vincent Rajkumar

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Final approval of manuscript: Martha Q. Lacy, Suzanne R. Hayman, Morie A. Gertz, Angela Dispenzieri, Francis Buadi, Shaji Kumar, Rafael Fonseca, Jacob B. Allred, Sumithra J. Mandrekar, S. Vincent Rajkumar

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EXHIBIT 5

52ND ASH® ANNUAL MEETING AND EXPOSITION
ORANGE COUNTY CONVENTION CENTER, ORLANDO, FL • DECEMBER 4-7, 2010
FINAL PROGRAM AND PERSONAL SCHEDULER

Last updated October 5, 2010. Please note that this site represents the latest program changes and differs from the print version in some details.

863 Pomalidomide Plus Low-Dose Dexamethasone In Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies In Dual-Refractory Disease

Oral and Poster Abstracts
Oral Session: Myeloma - Therapy, excluding Transplantation: Myeloma Phase I/II Trials and Correlative Studies

Monday, December 6, 2010: 7:15 PM
230 (Orange County Convention Center)

Martha Lacy, MD[1], *Sumithra Mandrekar, PhD*[2*], *Morie Abraham A Gertz, MD*[3], *Suzanne R. Hayman, MD*[1], *Kristen Detweiler Short, RN, CNP*[1*], *Francis Buadi, MD*[4], *Angela Dispenzieri, M.D.*[1], *Shaji Kumar, MD*[1], *Steven Zeldenrust, MD, PhD*[5*], *David Dingli, M.D., Ph.D.*[1], *Philip R. Greipp, MD*[3], *John Lust, MD, PhD*[3], *Stephen Russell, MD, PhD*[3*], *Robert Kyle, MD*[3], *Rafael Fonseca, MD*[6], *P. Leif Bergsagel, MD*[7], *Vivek Roy, MD*[8*], *A. Keith Stewart, MD*[9*], *Jacob Allred*[3*], *Kristina Laumann*[10*], *Craig B. Reeder, MD*[11], *S. Vincent Rajkumar, MD*[1*] *and Joseph R. Mikhael, MD*[9]

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[11]*Hematology, Mayo Clinic Arizona, Scottsdale, AZ*

Background: Patients with MM who have progressed after multiple novel agents have limited treatment options. Pomalidomide (CC4047) is the newest immunomodulatory (IMiD) agent. Pom/dex using a dose of 2 mg/day has demonstrated response rates (≥PR) of 63% in relapsed MM (Lacy, JCO 2009, 27:5008-5014) and 32% in a lenalidomide-refractory cohort (Lacy, Leukemia, in press). The maximum tolerated dose has been determined to be 4 mg/day for 21 of 28 days (Richardson, ASH, 2009), We opened two sequential phase II trials using the Pom/dex regimen at differing doses to study the efficacy of this regimen in patients who have failed both lenalidomide and bortezomib.

Methods: Patients refractory to both lenalidomide and bortezomib therapy; defined as relapsing on or within 60 days of stopping each regimen, were enrolled. Pomalidomide was given orally 2 mg daily (Cohort A) or 4mg daily (Cohort B) on days 1–28 of a 28-day cycle with oral dexamethasone given 40 mg daily on days 1, 8, 15 and 22. Response was assessed by the International **Myeloma** Working Group Uniform Response criteria. All patients received aspirin 325 mg daily for DVT prophylaxis.

Results: 35 patients with relapsed and resistant/refractory to both lenalidomide and bortezomib were enrolled in each cohort. The median age was 62 years (range, 39-77) in Cohort A and 61 (range, 45-77) years in Cohort B. The median time from diagnosis to enrollment was 57 months for Cohort A (range 12-249) and 72 months(range, 13-183) for Cohort B. 15 patients had high risk molecular markers in Cohort A and 16 in Cohort B. The median number of prior regimens was 6 in both groups. The median (range) duration on treatment was 5(1-13) and 2(0-6) cycles in cohorts A and B respectively. Toxicity at least possibly attributed to drug consisted primarily of myelosuppression: grade 3/4 neutropenia (37% Cohort A vs. 55% Cohort B); grade 3/4 thrombocytopenia (11% Cohort A vs. 13% Cohort B); and grade 3/4 anemia (9% Cohort A vs. 16% Cohort B). Grade 3/4 non-hematologic toxicities occurred in 23% Cohort A vs. 13% Cohort B. Grade 1 or 2 fatigue was the most common non-hematologic toxicity seen in 43% Cohort A vs. 52% Cohort B. Grade 1 or 2 neuropathy occurred in 17% Cohort A vs. 16% Cohort B. Other non-hematologic toxicities occurring in <5% included pneumonitis, hyperglycemia, renal failure, thrombosis. One patient in cohort B had grade 4 hepatitis. Confirmed responses in Cohort A consisted of VGPR 14%, PR 11%, and MR 24% (ORR 49%, 95% CI: 31-66), and responses in Cohort B consisted of VGPR 9%, PR 20%, and MR 12% (ORR 40%, 95% CI: 23-

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58). The median follow-up on alive patients was 7.5 months, and 3 months in Cohorts A and B, respectively. The median PFS in cohorts A and B are respectively 6.4 months (95% CI: 4.7-NR) and 3.3 months (95% CI: 2.3-NR).

Conclusions: Pom/dex is remarkably active and well tolerated in this heavily pre-treated population of dual bortezomib/lenalidomide-refractory MM patients. The majority of patients have not progressed and objective responses (MR or better) are seen in 40-49%. This study confirms therapeutic benefit for Pom/dex in patients relapsing after other novel therapies. These studies do not show an advantage for the 4 mg/day on days 1-28 of each 28 day cycle did not show an advantage over the 2 mg/day on days 1-28 of each 28 day cycle.

Table 1: Objective Responses

	2mg (n=35)	4mg (n=35)
VGPR	14%	9%
PR	11%	20%
MR	24%	12%
Overall (≥ MR)	49%	40%

Disclosures: Lacy: *Celgene:* Research Funding. **Gertz:** *Celgene:* Honoraria; *Millennium:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Dispenzieri:** *Celgene:* Honoraria, Research Funding; *Binding Site:* Honoraria. **Kumar:** *Celgene:* Consultancy, Research Funding; *Millennium:* Research Funding; *Merck:* Consultancy, Research Funding; *Novartis:* Research Funding; *Genzyme:* Consultancy, Research Funding; *Cephalon:* Research Funding. **Fonseca:** *Genzyme:* Consultancy; *Medtronic:* Consultancy; *BMS:* Consultancy; *AMGEN:* Consultancy; *Otsuka:* Consultancy; *Celegene:* Consultancy, Research Funding; *Intellikine:* Consultancy; *Cylene:* Research Funding; *Onyx:* Research Funding; *FISH probes prognostication in myeloma:* Patents & Royalties. **Bergsagel:** *Celgene:* Consultancy; *Centocor:* Consultancy; *Genentech:* Consultancy; *Amgen:* Consultancy; *Novartis:* Consultancy. **Stewart:** *Celgene:* Honoraria.

See more of: Myeloma - Therapy, excluding Transplantation: Myeloma Phase I/II Trials and Correlative Studies
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Group Art Unit: 1612
Serial No.: 12/229,074	Confirmation No.: 7450
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM 501872-999773)

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

1. Enclosures accompanying this Information Disclosure Statement are:

1a. ☒ A list of all patents, publications, applications, or other information submitted for consideration by the office.

1b. A legible copy of :

☐ Each publication or that portion which caused it to be listed on the PTO-1449;

☐ For each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion that have been checked to be unavailable at the USPTO's private PAIR system;

☐ An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report;

☐ Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language abstracts of the non-English language publications;

☐ All other information or portion which caused it to be listed on the PTO-1449.

1c. ☒ Pursuant to 37 C.F.R. § 1.98(a)(2)(ii), copies of the cited U.S. patents and U.S. patent application publications are not submitted herewith unless required by the office.

1d. ☐ Pursuant to 1287 OG 163, copies of cited pending unpublished applications that are available at the USPTO's private PAIR system are not submitted herewith.

2. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b):

☐ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);

☐ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application;

☐ Before the mailing of the first Office action on the merits;

☐ Before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

3. ☒ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application.

(Check either Item 3a or 3b)

3a. ☐ The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required.

3b. ☒ The $180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. §1.97(c) is:

☐ enclosed.

☒ to be charged to Jones Day Deposit Account No. 50-3013.

(Item 3b to be checked if any reference known for more than 3 months)

4. ☐ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee.

The Certification Statement in Item 5 below is applicable.

The $180.00 fee set forth in 37 C.F.R. §1.17(p) is:

☐ enclosed.

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5. ☐ Certification Statement (applicable if Item 3a or Item 4 is checked):

(Check either Item 5a or 5b)

5a. ☐ In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.

5b. ☐ Each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

5c. ☐ Pursuant to 37 C.F.R. §1.704(d), each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart application, and the communication was not **received** by any individual designated in 37 C.F.R. §1.56(c) more than thirty days prior to the filing of this information disclosure statement.

6. ☒ This application is a continuation application under 37 C.F.R. §1.53(b) or (d).

(Check appropriate Items 6a, 6b and/or 6c)

6a. ☐ A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith.

6b. ☒ Copies of publications listed on Form PTO-1449 from prior application Serial No. 10/438,213, filed on May 15, 2003, of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d).

6c. ☐ Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No. , filed on , and are provided herewith.

7. ☒ This is a Supplemental Information Disclosure Statement. (Check Item 7a)

7a. ☒ This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) supplements the Information Disclosure Statement filed on August 19, 2008.

8. ☐ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is:

(Check Item 8a, 8b, or 8c)

8a. ☐ Satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by the foreign office.

8b. ☐ Set forth in the application.

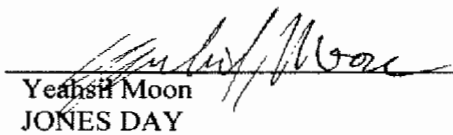
8c. ☐ Enclosed as an attachment hereto.

9. ☒ The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Jones Day Deposit Account No. 50-3013.

10. ☒ No admission is made that the information cited in this Statement is, or is considered to be, material to patentability and no representation is made that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: December 23, 2010



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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

Application Number	12/229,074
Filing Date	August 19, 2008
First Named Inventor	Jerome B. Zeldis
Art Unit	1612
Examiner Name	Simmons, Chris E.
Attorney Docket No.	9516-773-999

U.S. PATENT DOCUMENTS

*Examiner Initials	Cite No.	Document Number – Kind Code	Publication Date mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A83	7,435,745	10/14/2008	Celgene Corporation	
	A84	7,393,862	07/01/2008	Celgene Corporation	

FOREIGN PATENT DOCUMENTS

*Examiner Initials	Cite No.	Foreign Patent Document Country Code, Number, Kind Code (if known)	Publication Date mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	B01	WO 02/015926	02/28/2002	Kirin Beer Kabushiki Kaisha		
	B09	WO 92/14455	09/03/1992	The Rockefeller University		
	B10	WO 94/20085	09/15/1994	Children's Hospital Medical Center Corporation		

NON PATENT LITERATURE DOCUMENTS

*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	C205	"Celgene drug promises activity in solid tumors," Marketletter, June 18, 2001	
	C206	Meregalli et al., "High-dose dexamethasone as first line therapy of multiple myeloma?", Recenti Progressi in Medicina, 1998, 89(1):18-20	
	C207	Copy of Official Action in corresponding Canadian Application No. 2,476,983	
	C208	List, A., "New Approaches to the Treatment of Myelodysplasia," *The Oncologist*, 2002, 7(suppl. 1):39-49	
	C209	Kurzrock, R., "Myelodysplastic syndrome overview," *Seminars in Hematology* (Abstract only), 2002, 39(3)(suppl. 2):18-25 *Abstract only*	
	C210	Goerner, *et al.*, "Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias," *Biology of Blood and Marrow Transplantation* (Abstract only), 2002, 8(1):47-56	
	C211	Thomas, D., "Pilot studies of Thalidomide in Acute Myelogenous Leukemia, Myelodysplastic Syndromes, and Myeloproliferative Disorders," *Seminars in Hematology*, 2000, 37(1)(suppl. 3):26-34	
	C212	Zorat, F. *et al.*, "The clinical and biological effects of thalidomide in patients with myelodysplastic syndromes," *British Journal of Haematology*, 2001, 115:881-894	
	C213	Copy of Official Action dated February 10, 2009 in JP Application No. 2004-545192. (*English translation provided.*)	
	C214	Teramura, M., Men-ekiyokusei Ryouhou, *Current Therapy*, 2000, 18(5):140-144 (in Japanese)	√*
	C215	Kon-nichi no Chiryou Shishin, 1997 [Pocket Edition], Igaku Shoin, 1997, 513-514 (in Japanese)	√*
	C216	Okamoto, T., Kotsuzuiikeisei Shoukougun to Men-eki Ijo, Bessatsu Nihon Rinsho, Syndrome Series for each area, No. 22, Blood Syndromes III, Nihon Rinshou, 213-216 (in Japanese)	√*
	C217	Merck Manual, 17th ed. Japanese version, 1999, 951-952	√*

NYI-4336212v1

EXAMINER SIGNATURE	DATE CONSIDERED

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LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)		
	Application Number	12/229,074
	Filing Date	August 19, 2008
	First Named Inventor	Jerome B. Zeldis
	Art Unit	1612
	Examiner Name	Simmons, Chris E.
	Attorney Docket No.	9516-773-999

NON PATENT LITERATURE DOCUMENTS

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	C218	Copy of Notice of Allowance from U.S. Patent Application No. 11/096,155 dated January 12, 2010	
	C219	Rajkumar et al., "Combination therapy with thalidomide plus dexamethasone for newly diagnosed multiple myeloma," *American Society of Hematology*, 43rd Annual Meeting, Dec. 7-11, 2001, Abstract #3525	
	C220	Scheffler et al., "Safety and pharmacokinetics of CDC-501, a novel immunomodulatory-oncologic agent, after single then multiple, oral 100 mg twice daily doses," *American Society for Clinical Pharmacology and Therapeutics*, March 24-27, 2002, Abstract #WPIII-63	
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	C222	Kast, R.E., "Evidence of a mechanism by which etanercept increased TNF-alpha in multiple myeloma: New insights into the biology of TNF-alpha giving new treatment opportunities – the role of burproion," *Leukemia Research*, 2005, 29:1459-1463	
	C223	Tsimberidou, A. et al., "Pilot study of recombinant human soluble tumor necrosis factor (TNF) receptor (p75) fusion protein (TNFR:Fc;Enbrel) in patients with refractory multiple myeloma: increase in plasma TNFα levels during treatment," *Leukemia Research*, 2003, 27:375-380	
	C224	Dimopoulos, et al., "Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma," *Leukemia*, 2009, 1-6	
	C225	Hideshima, T., et al., "A review of lenalidomide in combination with dexathasone for the treatment of multiple myeloma," *Therapeutics and Clinical Risk Management*, 2008, 4(1):129-136	
	C226	Wang, M., et al., "Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma regardless of prior thalidomide exposure," *Blood*, 2008, 112(12):4445-4451	
	C227	Gandhi, A., et al., "Dexamethasone Synergizes with Lenalidomide to Inhibit Multiple Myeloma Tumor Growth, But Reduces Lenalidomide-Induced Immunomodulation of T and NK Cell Function," *Current Cancer Drug Targets*, 2010, 10(1):1-13	
	C228	Gay, F. et al., "Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients," *Blood*, 2010, 115(97):1343-150	
	C229	Richardson, P. *et al.*, "Thalidomide in multiple myeloma," *Biomed Pharmacother*, 2002, 56:115-28	
	C230	Swartz, G. *et al.*, "Pre-clinical evaluation of ENMD-0995: A thalidomide analog with activity against multiple myeloma and solid tumors," *Cell and Tumor Biology*, 2002, 43:181-182, Abstract# 910	
	C231	Mazucco, R., "Angiogenesis and Anti-angiogenesis Therapeutics," *IDrugs*, 2002, 5(4): 320-322	
	C232	Worker, C., "JP Morgan Hambrecht & Quist – 20th Annual Healthcare Conference," *IDrugs*, 5(2):113-116	
	C233	Treston, A. *et al.*, "Pre-Clinical Evaluation of a Thalidomide Analog with Activity Against Multiple Myeloma and Solid Tumors – ENMD-0995 (S-(-)-3-(3-amino-phthalimido)-glutarimide)," *Blood*, 2002, 100(11):816a, Abstract #3225	
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	C235	Fernandes, P., "Anti-Cancer Drug Discovery and Development Summit," *IDrugs*, 2002, 5(8):757-764	
	C236	Copy of Notification letter dated 8/30/10 from Natco Pharma Limited to Celgene Corporation re: Notification purusant to § 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act	
	C237	Copy of Complaint for Patent Infringement filed on 10/8/10 by Celgene Corporation in the U.S. District Court, District of New Jersey against Natco Pharma Limited	
	C238	Copy of Answer to Complaint filed on 11/18/10 by Natco Pharma Limited in the U.S. District Court, District of New Jersey	

NYI-4336212v1

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)		
	Application Number	12/229,074
	Filing Date	August 19, 2008
	First Named Inventor	Jerome B. Zeldis
	Art Unit	1612
	Examiner Name	Simmons, Chris E.
	Attorney Docket No.	9516-773-999

NON PATENT LITERATURE DOCUMENTS

*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	C239	Grosshans, E. and Illy, G., "Thalidomide Therapy for Inflammatory Dermatoses," *International Journal of Dermatology*, 1984, 23(9):598-602	
	C240	Krenn, M. *et al.*, "Improvements in Solubility and Stability of Thalidomide upon Complexation with Hydropropyl-β-Cyclodextrin," *Journal of Pharmaceutical Sciences*, 1992, 81(7):685-689	
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	C242	Schumacher, H. *et al.*, "The Teratogenic Activity of a Thalidomide Analogue, EM_{12}, in Rabbits, Rats, and Monkeys," *Teratology*, 1971, 5:233-240	
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	C244	Sheskin, J. and Sagher, F., "Trials with Thalidomide Derivatives in Leprosy Reactions," *Leprosy Review*, 1968, 39(4):203-205	
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	C248	Singhal, S. and Mehta, J., "Thalidomide in Cancer," *BioDrugs*, 2001, 15(3):163-172	
	C249	Copy of Notice of Opposition to EP 1 505 973 filed by Synthon B.V. on November 30, 2010	
	C250	Copy of Notice of Opposition to EP 1 505 973 filed by Strawman Limited on December 1, 2010	
	C251	Samson, D. *et al.*, "Infusion of Vincristine and Doxorubicin with Oral Dexamethasone as First-Line Therapy for Multiple Myeloma," *The Lancet*, 1989, 334(8668):882-885	
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	C253	Dimopoulos, M. *et al.*, "Thalidomide and dexamethasone combination for refractory multiple myeloma," *Annals of Oncology*, 2001, 12:991-995	
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	C257	Extracts from drug databases: retrieved from http://www.nextbio.com/b/search/ov/lMiD3%20cpd on 11/26/10 and http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=216326 on 11/26/10	

*cited in C213

NYI-4336212v1

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	12229074
Filing Date:	19-Aug-2008
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
Filer:	Yeahsil Moon/Rochelle Flowers
Attorney Docket Number:	9516-773-999

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1290**

Electronic Acknowledgement Receipt

EFS ID:	9112264
Application Number:	12229074
International Application Number:	
Confirmation Number:	7450
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
Customer Number:	84802
Filer:	Yeahsil Moon/Rochelle Flowers
Filer Authorized By:	Yeahsil Moon
Attorney Docket Number:	9516-773-999
Receipt Date:	23-DEC-2010
Filing Date:	19-AUG-2008
Time Stamp:	17:41:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1290
RAM confirmation Number	4500
Deposit Account	503013
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	EOT.pdf	24925 c35c173efe643dfb7324e73d8923a247c5de65b7	no	1
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	Amendment.pdf	637805 3ff5bdcea465d0b4fe08bc40e6565641026bdba0	no	14
Warnings:					
Information:					
3	NPL Documents	IDS_Reference_C222.pdf	362325 96905258748e98a35361824336cfc4813f36f358	no	6
Warnings:					
Information:					
4	NPL Documents	IDS_Reference_C223.pdf	431453 440be65f1bcd58b38c8027d2bef2bba163f04381	no	7
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	Exhibit_1_MacNeil.pdf	146698 d09e61db72fd22283ca991b2bcd9d037c022002a	no	2
Warnings:					
Information:					
6	Miscellaneous Incoming Letter	Exhibit_2_Lacy_Leukemia_2010.pdf	53375 4a1b174e7443b11d52a605baf2bf8cc8adf4b78c	no	2
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	Exhibit_3_Lacy_J_Clin_Oncol_2010.pdf	98903 025f116530fa8d8b12037002d32c4799e24f6926	no	3
Warnings:					
Information:					
8	Miscellaneous Incoming Letter	Exhibit_4_Lacy_J_Clin_Oncol_2009.pdf	617993 c7bd55e7ef052a791e19fa202412d9b3fd0b44f0	no	8

Warnings:					
Information:					
9	Miscellaneous Incoming Letter	Exhibit_5_Lacy_ASH_Abstract_2010.pdf	142356 dfa58d5dce1544021461fe89dfec7bd7b957bdaf	no	3
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Filed (SB/08)	IDS.pdf	357584 6959d169ec0e65828a92f931bbcfdf1b9f3ce746	no	6
Warnings:					
Information:					
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11	Fee Worksheet (PTO-875)	fee-info.pdf	32246 5d3f9ae3cf3aa5fdc45f52ff69cb3aa957193de0	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2905663		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Group Art Unit: 1612
Serial No.: 12/229,074	Confirmation No.: 7450
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM 501872-999773)

PETITION FOR EXTENSION OF TIME UNDER 37 CFR § 1.136(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

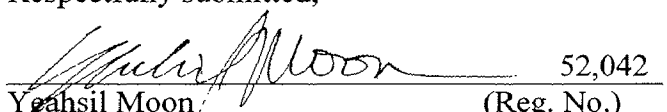
Sir:

It is respectfully requested that the time for response to the Office Action dated June 24, 2010 be extended for a period of 3 months from September 24, 2010, to and including December 27, 2010.

The fee for this extension is estimated to be $1,110.00. Please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: December 23, 2010



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PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/229,074	Filing Date 08/19/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/23/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 35	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/JULIET MCMILLAN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

84802 7590 08/09/2011

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1612	
MAIL DATE	**DELIVERY MODE**
08/09/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	12/229,074	ZELDIS, JEROME B.
	Examiner	Art Unit
	CHRIS SIMMONS	1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-56* is/are pending in the application.

4a) Of the above claim(s) *31 and 54-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30 and 32-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 12/23/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Applicant's arguments, see page 7, 2nd full paragraph, filed 12/23/2010, with respect to the rejections of the claims under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of prior art teaching immunomodulatory activity of thalidomide and pomalidomide and immunomodulatory effects with regard to possible treatment of MM patients.

Applicant's arguments, see pages 12 to 13, filed 12/23/2010, with respect to double patenting have been fully considered and are persuasive. The rejections of the claims have been withdrawn.

Claim Rejections - 35 USC § 103

1) Claims 22, 23, 29, 30, 32-35 and 37-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyle et al. (Seminars in Oncology (Dec 2001);28(6):583-7)

in view of Davies et al. (cited as C35 in 08/19/2008 IDS), and Corral et al. (cited as C34 in 08/19/2008 IDS) as evidenced by Muller et al. (cited as C14 in 08/19/2008 IDS).

Kyle et al. disclose methods for treating multiple myeloma (MM) by cyclically administering thalidomide (Thal) and dexamethasone (Dex). Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. The dosage amounts of Thal had to be adjusted in some patients after signs of toxicity appeared. Signs of toxicity showed in some patients receiving 400 mg/day of thalidomide and the dosage had to be decreased (see first paragraph on page 587). Kyle further teaches Thal should be discontinued if a rash occurs and then resumed at a lower dose after the rash has resolved (page 584, column 1, 1st full paragraph). The addition of Dex to Thal may produce a response in patients who are refractory to Thal. Kyle et al. disclose Dex plus Thal produces an objective response in approximately ¾ of previously untreatable MM patients (page 587, first column, top paragraph). Thalidomide may be used to treat MM in combination biological agents such as alpha2-interferon, i.e., immunotherapy (see Table 2 at page 586). Kyle does not expressly teach pomalidomide.

Davies et al. discloses that Thal and Thal analogues induce a dose-dependent inhibition of proliferation in MM cell lines and patient MM cells resistant to conventional

chemotherapy, and they add to the effect of Dex (see page 210, first column, lines 11-14). Davies et al. discloses that Thal and Thal analogues increase the production of IL-2 and INF-gamma. They suggest that Thal (200-800 mg/day; See page 211, column 2, third paragraph from bottom) and the analogues can treat MM by increasing the killing of the MM cancer cells by natural killer T cells ("NK cells") since the NK cells are modulated by IL-2 and INF-gamma (See page 210, second column, last sentence bridging to page 211, first column, first paragraph; also see page 216 column 1, lines 4-6 and column 2, lines1-9 and last sentence). Davies et al disclose that Thal and the analogues may also treat MM by inhibiting the growth and survival of MM cells since Thal and the analogues abrogate the up-regulation of IL-6, a major growth factor and survival factor in MM (see page 215, lines 1-12). The analogues are more potent inducers of T-cell proliferation with IFN-gamma and IL-2 secretion (IFN-gamma and IL-2 being modulators of NK cells) and inhibitors of IL-6 secretion from PBMCs (IL-6 being a growth factor for MM cells) (see page 210, column 2, first paragraph, last sentence). The authors concluded that their results show that Thal and its analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity (page 216, column 2, last sentence). Davies et al. do not expressly teach pomalidomide as a specific Thal analogue, cyclical treatment thereof, or a dose of 5-50 mg/day.

Corral et al. disclose that analogues of Thal were tested to find more potent agents with decreased teratogenic potential when compared to Thal (see page 383,

column 2, first sentence, last paragraph). Corral et al. disclose that compound CI-A (i.e., structure 5a as evidenced at page 1626 of Muller et al., which is the claimed structure for pomalidomide in claims 22 and 23; see Corral et al., page 381, column 1, last sentence of first full paragraph) is an immunomodulatory Thal analogue that is a more potent inducer of IL-2 and INF-gamma production (see Fig. 3 at page 383) and an inhibitor of IL-6 production (see page 382, Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the oral treatment of MM with a combination of Thal with Dex as described by Kyle et al. by replacing Thal with pomalidomide. The motivation would have been to take advantage of the increased potency of pomalidomide in inducing IL-2 and INF-gamma production as outlined by Corral et al, since increasing the production of IL-2 and INF-gamma are suggested to be useful to treat MM by increasing the lysis (I.e., killing) of MM cells by NK cells, as it is outlined by Davies et al. The motivation would have also been to take advantage of the inhibitory functions of pomalidomide on the production of IL-6, as described by Corral et al., since IL-6 is a major growth factor and survival factor for MM cells, as outlined by Davies et al. Decrease of IL-6 would deprive the MM cancer cells of a major growth and survival factor.

Because of the increased potency of pomalidomide relative to Thal in inducing IL-2 and INF-gamma production, one of ordinary skill would have been motivated to use pomalidomide at a lower dosage amounts compared to Thal to achieve therapeutic responses with less potential for known side effects caused by Thal. Furthermore, motivation to alter the therapeutic regimen is disclosed by Kyle who further teaches Thal

should be discontinued if a rash occurs and then resumed at a lower dose after the rash has resolved (page 584, column 1, 1st full paragraph). One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects. The magnitude of a prophylactic or therapeutic dose of each active ingredient in the acute or chronic management of MM will vary with the specific active ingredients and the severity of disease. The dose, and perhaps the dose frequency, may also vary according to age, body weight, response, and recurrence of symptomology. Accordingly, the differences in claimed amount from the amounts disclosed in Kyle et al. and Davies et al. will not support the patentability unless there is evidence indicating such amount is critical. See MPEP 2144.05[R-5] II A.

2) Claims 24-28, 36 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyle et al. (Seminars in Oncology (Dec 2001);28(6):583-7) in view of Davies et al. (cited as C35 in 08/19/2008 IDS), and Corral et al. (cited as C34 in 08/19/2008 IDS) as evidenced by Muller et al. (cited as C14 in 08/19/2008 IDS), the combination as applied to the claims above taken further in view of US 6,555,554 (previously cited by Examiner 06/24/2010).

The disclosures for Kyle, Davies, Corral and Muller are outlined above. Their combination does not expressly teach salts, solvates or stereoisomers of pomalidomide. The combination does not expressly teach capsules, tablets or the particular excipients enumerated in claim 53.

The US '554 patent discloses a composition comprising pomalidomide (Examples 14 and 15), its salt, or its R- or S-configuration enantiomers, in a single or multidose regimen to reduce TNF-alpha and to improve oncogenic or cancerous conditions. The composition can be in the form of a capsule or tablet. See claims 1-5 and 9-17. Excipients including microcrystalline may be added to the composition (see column 8, lines 31-32).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to treat MM with pomalidomide as suggested by Kyle Davies, Corral and Muller by administering pomalidomide, its salt, solvate, or enantiomerically pure configurations in a tablet or capsule containing an excipient such as microcrystalline cellulose. The artisan would have had a reasonable expectation that the use of such a tablet or capsule containing the different form of pomalidomide would have provided pomalidomide to the patient for the treatment of MM.

It would have been obvious to use the solvate form of pomalidomide as well because the structure of pomalidomide and the solvate of pomalidomide are structurally similar compounds and would reasonably been expected to share similar therapeutic effects.

Response to Arguments

The rejection has been changed significantly. As such Applicant's arguments on page 6 to page 10 are rendered moot.

Applicant has presented MacNeil, 2010 (Exhibit 1); Lacy et al., Leukemia, 2010 (Exhibit 2); Lacy et al., J. Clin. Oncol., 2010 (Exhibit 3); Lacy et al., J. Clin. Oncol., 2009 (Exhibit 4); and Lacy et al., ASH Abstract #863, 2010 (Exhibit 5) and alleges they support the case for a showing of unexpected results. Particularly, Applicant alleges MacNeil reports on monotherapy of pomalidomide combined with dexamethasone in MM patients with response rates of 50% or better in heavily pretreated patients.

The Examiner does not find Applicant's assertion that MacNeil supports a showing of unexpected results. The Examiner would submit that MacNeil does not state there was a response rate of 50% or better; MacNeil simply makes a statement that 53% of patients responded after dexamethasone was added. This is not the same as response rates. MacNeil actually states that the confirmed response rate was 32% (see last column, 2nd full paragraph) not 50% or better as alleged by Applicant. Furthermore, the rejection is based on replacing Thalidomide used in combination with dexamethasone with pomalidomide. The comparison described by MacNeil is between pomalidomide alone versus pomalidomide with dexamethasone. This does not show how promalidomide with dexamethasone compares to thalidomide with dexamethasone. As such, the Examiner does not find that the comparison relates to the closest prior art.

Applicant argues the Lacy publications (Exhibits 2-5) support a showing of unexpected results. Particularly, Lacy discussed that studies showed the impressive activity of pomalidomide in patients who were refractory to other agents including thalidomide.

The Examiner does not find this to be persuasive because Corral already acknowledges the increased potency of pomalidomide as an inducer of IFN-gamma and IL-2 production which would make it a more potent inducer of NK cells which lyse MM cells as outlined above.

Applicant also states that Lacy concluded that the therapy was extremely active and well tolerated in treatment of relapsed/refractory MM. The Examiner does not find this argument to be persuasive because merely showing that therapy was extremely active and well tolerated in treatment of relapsed/refractory MM does not represent anything unexpected or surprising.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/CHRIS SIMMONS/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12229074	ZELDIS, JEROME B.
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	CHRIS E SIMMONS	1612

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
GOOGLE, EAST, PUBMED, INVENTOR SEARCHES COMPLETE	06/14/2010	CSIMMONS
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INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

Notice of References Cited	Application/Control No. 12/229,074	Applicant(s)/Patent Under Reexamination ZELDIS, JEROME B.	
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	U	Kyle et al. (Seminars in Oncology (Dec 2001);28(6):583-7).
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Therapeutic application of thalidomide in multiple myeloma.

Kyle RA, **Rajkumar SV**.

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Treatment with thalidomide and dexamethasone was given to 26 patients with active, previously untreated multiple myeloma (MM). Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Response was defined as a decrease in serum and urine monoclonal (M)-protein by 50% or greater. Twenty (77%) of 26 patients with active MM exhibited a therapeutic response. Among the first seven patients treated with a thalidomide dose of 400 mg, grade III to IV skin toxicity developed in two. Drug titration was then stopped and the thalidomide dose maintained at 200 mg/d. Six (86%) of seven patients showed a response after thalidomide dose escalation, whereas 14 (74%) of 19 patients demonstrated a response with a constant thalidomide dose of 200 mg/d. Thalidomide alone produced a response in six (38%) of 16 patients with smoldering or indolent myeloma. The angiogenesis grade was elevated in only 8% of these patients. Thirty-two patients with relapsed myeloma were treated with thalidomide dosed at 200 mg/d, with 200-mg escalations every 2 weeks to a maximum daily dose of 800 mg. Prior chemotherapy had failed and five (16%) patients had experienced relapse following stem cell transplantation. Ten (38%) of the 26 patients who had received at least two cycles of therapy obtained a response. Copyright 2001 by W.B. Saunders Company.

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Therapeutic Application of Thalidomide in Multiple Myeloma

Robert A. Kyle and S. Vincent Rajkumar

Treatment with thalidomide and dexamethasone was given to 26 patients with active, previously untreated multiple myeloma (MM). Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Response was defined as a decrease in serum and urine monoclonal (M)-protein by 50% or greater. Twenty (77%) of 26 patients with active MM exhibited a therapeutic response. Among the first seven patients treated with a thalidomide dose of 400 mg, grade III to IV skin toxicity developed in two. Drug titration was then stopped and the thalidomide dose maintained at 200 mg/d. Six (86%) of seven patients showed a response after thalidomide dose escalation, whereas 14 (74%) of 19 patients demonstrated a response with a constant thalidomide dose of 200 mg/d. Thalidomide alone produced a response in six (38%) of 16 patients with smoldering or indolent myeloma. The angiogenesis grade was elevated in only 8% of these patients. Thirty-two patients with relapsed myeloma were treated with thalidomide dosed at 200 mg/d, with 200-mg escalations every 2 weeks to a maximum daily dose of 800 mg. Prior chemotherapy had failed and five (16%) patients had experienced relapse following stem cell transplantation. Ten (38%) of the 26 patients who had received at least two cycles of therapy obtained a response.

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THALIDOMIDE WAS introduced more than 40 years ago as a sedative and then used for nausea and vomiting of pregnancy. Its teratogenic effects were manifested by the development of phocomelia. Fortunately the drug was not approved in the United States.

Thalidomide was subsequently found to be beneficial for the treatment of erythema nodosum leprae and it has been approved for this purpose in the United States. It is also useful in the treatment of cachexia from acquired immunodeficiency syndrome (AIDS), aphthous ulcers from Behcet's disease, and in the treatment of chronic graft-versus-host disease.[1] It was reported to be beneficial in one third of patients with multiple myeloma (MM) who were refractory to therapy.[2]

MECHANISM OF ACTION

The mechanism of action of thalidomide in MM is unclear. It has both immunomodulatory as well as antiangiogenic effects. It inhibits the production of tumor necrosis factor-alpha (TNF-α) by increasing the degradation of TNF-α mRNA. It also increases the effect of α_1-acid glycoproteins, which have anti–TNF-α activity. Thalidomide also stimulates cytotoxic T-cell proliferation and increases the secretion of interferon-gamma and interleukin-2 (IL-2). It also increases T-helper cell type 2 (Th2) cytokine production and inhibits T-helper cell type 1 (Th1) production. It also modulates the expression of the adhesion molecules on the surface of the cell.

Thalidomide also has potent antiangiogenic properties. This is probably accomplished by blocking the action of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Thalidomide has been shown to decrease the vascular density of murine Lewis lung tumors, resulting in a reduction of metastasis. In addition, thalidomide inhibits the microvessel formation in the rat aortic ring assay in the presence of human or rabbit liver microsomes and slows human aortic endothelial cell proliferation. It is not known whether the immunomodulating effects or its antiangiogenic activity accounts for its therapeutic role in MM. In vitro addition of thalidomide to human myeloma cell lines or human myeloma cells leads to no significant changes in apoptosis or secretion of VEGF.[3]

In humans, oral thalidomide appears to be well absorbed with peak concentration achieved at approximately 4 hours. It is widely distributed throughout the body and undergoes rapid hydrolytic cleavage resulting in more than 20 metabolites. These metabolites are quickly excreted in the

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urine. The effects of renal or hepatic dysfunction on the clearance of thalidomide are not known.[4]

Adverse side effects of thalidomide include sedation and constipation. Sensorimotor peripheral neuropathy is a major problem in some patients. It consists of symmetric paresthesias usually beginning in the toes and extending to the feet and legs. The hands may also be involved. Older patients appear to be more susceptible to neuropathy. The neuropathy is axonal and usually improves with cessation of thalidomide but the symptoms may persist. Carpal tunnel syndrome may occur. Hypotension and bradycardia may also occur. Headache, dizziness, and mood changes have been reported. Dryness of the skin, pruritus, and rash occur in approximately one fourth of patients. The drug should be discontinued if a rash occurs and then resumed at a lower dose after the rash has resolved. Stevens-Johnson syndrome has been seen in patients receiving thalidomide and dexamethasone.[5] Hypothyroidism and thrombotic episodes have been reported with the use of thalidomide.[6]

Thalidomide is contraindicated in pregnant women. All women of childbearing age must be registered with the System for Thalidomide Education and Prescribing Safety (STEPS) Program. Women of childbearing age must have a pregnancy test before starting therapy and every 2 to 4 weeks thereafter. They must use two effective contraceptive methods while males must use a condom or have a vasectomy.

THALIDOMIDE IN REFRACTORY MULTIPLE MYELOMA

Singhal et al at the University of Arkansas reported benefit in a group of heavily pretreated patients with MM.[2] Eighty-four previously treated patients with refractory myeloma were given thalidomide for a median of 80 days. Many of the patients had relapsed following autologous stem cell transplantation. The dosage was started at 200 mg/d and increased as tolerated in 200-mg increments every 2 weeks to a maximum of 800 mg/d. The serum or urine monoclonal (M)-protein levels decreased by 50% or more in 21 patients. Six additional patients had at least a 25% reduction with a total response rate of 32%. The median time to response was 1 month, with the reduction in M-protein occurring within 2 months in 78%. The responses were associated with a decreased number of bone marrow plasma cells and an increase in hemoglobin level. Eighty-one percent of the 48 patients who had repeated bone marrow studies after thalidomide therapy had a reduction in plasma cells. Anemia and bone pain improved. The median duration of response has not been reached after 14.5 months of follow-up. Thalidomide was used because of it antiangiogenesis properties, but the microvascular density of the bone marrow did not change significantly in patients who responded. Mild or moderate constipation, weakness or fatigue, or somnolence occurred in one third of patients.

We reported a 25% response rate in 16 patients with relapsed MM.[7] Thalidomide was given orally in a dose of 200 mg/d for 2 weeks and then increased by 200-mg/d increments every 2 weeks up to a maximum of 800 mg/d. All patients had received two or more previous chemotherapeutic regimens. Four patients had relapsed following autologous stem cell transplantation. Four patients obtained a partial response (reduction of M-protein in the serum or urine of $\geq$50% and a similar reduction of soft tissue plasmacytomas if present). No patients had a complete response. Six patients had stable disease. The median tolerated dose of thalidomide was 400 mg/d. The major side effects included constipation, excessive sedation, fatigue, and rash. One patient developed peripheral neuropathy.[7] A subsequent phase II study conducted at the Mayo Clinic included 32 patients.[8] Twenty-six patients were evaluable at last report. All had received at least two cycles of therapy. The response rate was 38%, but no complete responses were seen. Neuropathy occurred in 10%. The angiogenesis grade was high in 52%, intermediate in 30%, and low in 18%. No significant changes in microvessel density (MVD) occurred in the responders. In addition, the pretreatment MVD and angiogenesis grade did not appear to be associated with response to therapy. It was found that response rates were significantly higher in patients with a high plasma cell labeling index (PCLI) ($\geq$1%) compared to those with a low PCLI—57% versus 21%, $P = .02$.[8]

In another report,[9] 47 patients with resistant myeloma were treated with thalidomide 200 mg/d, which was increased in 200-mg increments every 14 days, in the absence of severe side effects, to a maximum dosage of 800 mg/d. In addition, the patients were given dexamethasone 20 mg/m^2 on

days 1 to 5 and 15 to 18. Responding patients were maintained on the maximally tolerated dose of thalidomide and dexamethasone on days 1 to 5 of each month. A partial response (>50% serum M-protein reduction and/or >75% of Bence Jones protein reduction) occurred in 24 of 47 patients (52%). The median time to remission was 1 month. Responses occurred in 12 patients who had been resistant to regimens containing high-dose dexamethasone or thalidomide given as a single agent. The response occurred in 55% of 20 patients with primary refractory disease and in 48% of 27 patients who were in refractory relapse. The projected median remission duration was greater than 10 months. Neuropathy occurred in 43% while deep venous thrombosis and occasional pulmonary embolus occurred in 11%.[9]

Eighty-three patients with MM from 10 French centers were treated with thalidomide. Fifty-eight patients had received either a single or double autologous stem cell transplant while 23 had received chemotherapy alone. All had active MM. The β_2-microglobulin value was greater than 4 g/L in 39, hemoglobin less than 9 g/dL in 34, and platelet count less than 50,000/μL in 17. The median initial dose of thalidomide was 400 mg/d and was increased by 100- or 200-mg increments if tolerated. The median dose received was 373 mg/d. Responses occurred in 55 patients (66%): major response in 11, partial response in 28, and minor response in 16. Fifteen patients progressed, while 13 remained stable. Nine of 55 responders subsequently relapsed. A univariate analysis revealed that performance status greater than 1, patients requiring blood transfusion, and platelet counts less than 50,000/μL are associated with lower risk of overall and event-free survival. In multivariate analysis, only a platelet count of less than 50,000/μL was associated with a shorter risk of event-free and overall survival. They concluded that thalidomide was ineffective in patients with very advanced disease especially those with thrombocytopenia less than 50,000/μL.[10]

The combination of clarithromycin (Biaxin, Abbott Laboratories, Abbott Park, IL), thalidomide, and dexamethasone has been reported as a highly effective combination. Twenty-six patients with MM and six with Waldenström's macroglobulinemia were given Biaxin 500 mg twice daily, thalidomide 50 mg daily, escalated to a maximum of 200 mg and dexamethasone 40 mg every 2 weeks. A response was reported in all 24 evaluable patients.[11] The role of Biaxin in this regimen needs to be clarified.

Table 1. Activity of Thalidomide in Relapsed Multiple Myeloma

Study	No. of Patients	Response Rate %
Singhal et al[2]	84	32
Weber et al[14]	44	25
Durie and Stepan[15]	33	24
Juliusson et al[16]	23	43
Kneller et al[17]	17	65
Rajkumar et al[7]	16	25
Shima et al[18]	13	54
Neben et al[19]	11	27
Sabir et al[20]	10	70
Cheng et al[21]	9	78
Schiller et al[22]	8	50

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Results of therapy with thalidomide in several series of relapsed MM are shown in Table 1.[12] At the Mayo Clinic, we are evaluating the role of single-agent thalidomide in patients with newly diagnosed, asymptomatic smoldering MM. We are also using the combination of thalidomide plus dexamethasone for newly diagnosed symptomatic patients. The effect of thalidomide on bone marrow angiogenesis and the expression of VEGF, bFGF, and their receptors are being done. A randomized trial of thalidomide plus dexamethasone versus dexamethasone alone for newly diagnosed symptomatic myeloma is being developed by the Eastern Cooperative Oncology Group.

THALIDOMIDE PLUS DEXAMETHASONE AS FIRST-LINE THERAPY

A phase II trial of thalidomide and dexamethasone was given as first-line therapy to 26 patients with active MM.[13] Thalidomide was given orally as a dose of 200 mg/d for 2 weeks and then increased as tolerated by 200 mg/d every 2 weeks to a maximum dose of 800 mg/d. Dexamethasone was given orally at a dose of 40 mg/d on days 1 to 4, 9 to 12, and 17 to 20 for odd cycles and 40 mg/d on days 1 to 4 for even cycles and repeated at monthly intervals. Response was defined as a decrease in

serum and urine M-protein of 50% or greater. Twenty-six patients with active MM were treated. In the thalidomide/dexamethasone arm, two patients had grade 3 or 4 skin toxicity among the first seven patients treated at a thalidomide dosage of 400 mg/d. The thalidomide/dexamethasone arm was then amended to stop dose escalation and keep thalidomide at a dosage of 200 mg/d. Twenty of 26 patients (77%) obtained an objective response. The response rate was 86% with thalidomide dose escalation (6/7 patients) and 74% with thalidomide dose constant at 200 mg (14/19 patients). Major grade 3 or 4 toxicities included rash in three patients, and sedation, constipation, and myalgias in one patient each. The median pretreatment MVD was 27, while the angiogenesis grade was high in 64%. The PCLI was greater than 1% in 67%, 9%, and 0% with high-, intermediate-, and low-grade angiogenesis, respectively. No significant changes were observed in MVD following treatment. The pretreatment MVD and angiogenesis grade did not appear to be associated with response to therapy. This study demonstrated that thalidomide/dexamethasone can be effective as first-line therapy and merits further study as an oral alternative to infusional vincristine, doxorubicin, and dexamethasone (VAD) for newly diagnosed patients with active MM. In this study patients who are candidates for stem cell transplantation are being harvested after four cycles of thalidomide/dexamethasone. Thus far, there have been no significant problems with stem cell mobilization with this regimen, but it is being evaluated.

Thalidomide is being evaluated for patients with newly diagnosed myeloma as part of the Total Therapy II regimen at the University of Arkansas. The investigators are also studying the role of post-transplant maintenance with thalidomide. Several other institutions have ongoing clinical trials investigating the role of thalidomide in myeloma. Potential strategies for the use of thalidomide are summarized in Table 2.[12]

Thalidomide has also been used for patients with smoldering multiple myeloma (SMM). SMM is defined as a M-protein of ≥3 g/dL or bone marrow plasma cell value ≥10% but no evidence of anemia, hypercalcemia, renal insufficiency, lytic bone lesions, or extramedullary plasmacytomas. These patients have a higher risk of transformation to MM than those with monoclonal gammopathy of undetermined significance (MGUS). However, many SMM patients can be observed without therapy for months or years; close follow-up is recommended.

Table 2. Potential Strategies for Thalidomide in Multiple Myeloma

- Combination with dexamethasone
- Combination with VAD in preparation for high-dose therapy and transplantation
- Combination with melphalan and prednisone for patients who are not transplant candidates
- Single-agent thalidomide therapy for patients with smoldering myeloma

Plateau phase

- Maintenance therapy following autologous stem cell transplantation

Relapsed myeloma

- Thalidomide as a single agent
- Combination of thalidomide with dexamethasone
- Combination of thalidomide with chemotherapy
- Combination of thalidomide with biological agents such as α_2-interferon

Reprinted with permission from PRR, Inc. Rajkumar SV: Thalidomide in multiple myeloma. ONCOLOGY 14(12): Supplement No. 13, 1-15, 2000.

Thalidomide was given at a dosage of 200 mg/d for 2 weeks and then increased as tolerated by 200 mg/d every 2 weeks to a maximum dose of 800 mg/d. Response was defined as a decrease in serum and urine M-protein by 50% or greater. Six of 16 patients (38%) achieved a response. The median pretreatment MVD was 7, while the angiogenesis grade was high in only 8%. It was concluded that patients with SMM achieved significant response with thalidomide alone but these results are preliminary and need further confirmation.[13] Furthermore, the goal of treatment in SMM is delay in progression to active MM. Thus, unless randomized trials show that thalidomide can delay time to progression, it cannot be recommended as treatment for SMM outside the setting of appropriate clinical trials.

CONCLUSION

Thalidomide is a useful agent for treatment of patients with refractory MM. Approximately one third of patients will obtain an objective response.

The addition of dexamethasome to thalidomide may produce a response in patients who are refractory to thalidomide. The doseage must be altered depending upon the side effects. Dexamethasome plus thalidomide produces an objective response in approximately three fourths of previously untreated MM patients. There have been no problems with stem cell collection following 3 to 4 months of therapy and engraftment of autologous stem cell transplantation has been satisfactory. We conclude that thalidomide is a useful agent in MM.

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EAST Search History

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L7	5	(("5,635,517") or ("6,555,554") or ("6,281,230")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/30 20:26
L8	18	(celgene.as. or zeldis.in.) myeloma.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/07/30 20:26
L9	51	(celgene.as. or zeldis.in.) myelo$.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/07/30 20:26
L10	8	(("7119106") or ("7189740") or ("6,281,230") or ("6,555,554") or ("7,393,862")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/30 20:26
L11	2	("7,119,106").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/30 20:26
L12	4	(("7,393,862") or ("7,189,740")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/30 20:26
L13	10	(("7351729") or ("20080207644") or ("20090252710") or ("20100092489") or ("20090317456")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/30 20:26
L14	30471	multiple adj myeloma actimid pomalidomide "4047"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/07/30 20:26
L15	10	L13 L14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/07/30 20:26
L16	30499	multiple adj myeloma Actimid pomalidomide "4047" "cc4047"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/07/30 20:26
L17	10	L13 L16	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/07/30 20:26

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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

Application Number	12/229,074
Filing Date	August 19, 2008
First Named Inventor	Jerome B. Zeldis
Art Unit	1612
Examiner Name	Simmons, Chris E.
Attorney Docket No.	9516-773-999

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*Examiner Initials	Cite No.	Document Number – Kind Code	Publication Date mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	B09	WO 92/14455	09/03/1992	The Rockefeller University		
	B10	WO 94/20085	09/15/1994	Children's Hospital Medical Center Corporation		

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NYI-4336212v1

EXAMINER SIGNATURE /Chris Simmons/	**DATE CONSIDERED** 07/30/2011

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	C238	Copy of Answer to Complaint filed on 11/18/10 by Natco Pharma Limited in the U.S. District Court, District of New Jersey	

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	Filing Date	August 19, 2008
	First Named Inventor	Jerome B. Zeldis
	Art Unit	1612
	Examiner Name	Simmons, Chris E.
	Attorney Docket No.	9516-773-999

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Confirmation No.: 7450
Serial No.: 12/229,074	Group Art Unit: 1612
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM: 501872-999773)

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to Office Action dated August 9, 2011, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application. Submitted herewith is Petition for extension of term from November 9, 2011 to and including January 9, 2012 with fee.

Amendments to the Claims are reflected in the listing of the claims that begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

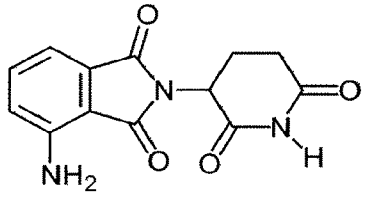
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

Claims 1-46. (canceled)

47. (currently amended) A method of treating multiple myeloma, which comprises administering orally to a patient having multiple myeloma from about [[0.5]] 1 mg to about 4 mg per day of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of the formula:



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or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically effective amount of dexamethasone, wherein the multiple myeloma is relapsed, refractory or resistant to previous therapy.

48. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about [[0.5]] 1 mg to about 4 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 of each cycle.

49. (previously presented) The method of claim 47, wherein the compound is orally administered in an amount of 2 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 every 28 days.

50. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about [[0.5]] 1 mg to about 4 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 every 28 days.

51. (previously presented) The method of claim 47, wherein the compound is orally administered in an amount of 2 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 every 28 days.

52. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about [[0.5]] 1 mg to about 4 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once weekly.

53. (previously presented) The method of claim 36, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

54-56. (canceled)

57. (new) The method of claim 47, wherein the previous therapy is treatment with thalidomide, lenalidomide, bortezomib, dexamethasone, carfilzomib, stem cell transplantation, or a combination thereof.

58. (new) The method of claim 47, wherein the compound is administered orally.

59. (new) The method of claim 58, wherein the compound is administered in the form of a capsule or tablet.

60. (new) The method of claim 47, wherein the compound is administered in an amount of about 2 mg per day.

REMARKS

I. Amendments to the Claims

Claims 1-21 were previously canceled, and claims 22-46 and 54-56 are canceled without prejudice. Claims 47, 48, 50 and 52 are amended to clearly define the subject matter of the invention. New claims 57-60 are added. No new matter has been added. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

II. The Claimed Invention is Not *Prima Facie* Obvious

The rejection over the combination of Kyle, Davies, Corral and Muller

Claims 22, 23, 29, 30, 32-35 and 37-52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kyle *et al.* (*Sem. Oncology*, 2001, "Kyle") in view of Davies *et al.* (*Blood*, 2001, "Davies"), Corral *et al.* (*J. Immuno.*, 1999, "Corral") and Muller *et al.* (*Bioorg. Med. Chem. Lett.*, 1999, "Muller"). (Pages 2-6 of the Action). Applicant respectfully traverses the rejection.

The Office alleges that Kyle discloses methods for treating multiple myeloma ("MM") with thalidomide and dexamethasone (page 3 of the Action). The Office also alleges that Davies discloses that thalidomide analogues can treat MM as more potent inducers of T cell proliferation with IFN-gamma and IL-2 secretion, and inhibitors of IL-6 secretion (pages 3-4 of the Action). It is alleged that Corral discloses thalidomide analogue that is a more potent inducer of IL-2 and IFN-gamma production, and an inhibitor of IL-6 production (pages 4-5 of the Action). It is further alleged that Muller discloses pomalidomide structure (page 5 of the Action).

Thus, the Office alleges that it would have been obvious to one of ordinary skill in the art to modify the treatment of MM using a combination of thalidomide with dexamethasone by replacing thalidomide with pomalidomide. Page 5 of the Action. Applicant respectfully disagrees.

The claimed methods require at least: (1) using the specific amounts (1 to 4 mg/day) of the recited compound, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (also known as "pomalidomide"), (2) for treating specific multiple myeloma (relapsed, refractory or resistant to previous therapy), (3) in combination with dexamethasone, and (4) by administering them in particular dosing regimens.

Applicant respectfully points out that the PTO bears the burden of establishing a case of *prima facie* obviousness against the claims as a whole. That is, all the claim

elements must be considered in a 103 rejection. As discussed in detail below, Applicant respectfully submits that the cited references would not have provided any reason to specifically select the combination of the specific drugs in specific amounts for treating particular multiple myeloma, much less the claimed methods using the specific dosing regimens.

First, Kyle appears to be a review article that discusses previous trials using thalidomide alone in treating refractory multiple myeloma, and thalidomide plus dexamethasone as first-line therapy in treating multiple myeloma. On page 586, last paragraph to page 587, first paragraph, Kyle concludes that thalidomide is a useful agent for treating refractory multiple myeloma since approximately one third of patients will obtain an objective response. However, patients remain refractory to thalidomide, and according to Kyle, some of those refractory patients may respond to thalidomide plus dexamethasone:

> The addition of dexamethasone to thalidomide may produce a response in patients who are refractory to thalidomide. [Emphasis added.] [*Kyle*, at page 587].

Thus, Kyle concludes, at best, that thalidomide may be useful in the treatment of multiple myeloma. The reference does not state, as the PTO seems to suggest, that the thalidomide plus dexamethasone combination is better than thalidomide alone. For example, the response rate of using thalidomide alone in retractory multiple myeloma reported in a Cheng study is 78% (page 585, Table 2), while the response rate of the combination of thalidomide with dexamethasone is 77% (page 586, Column 1). That is, no difference by the addition of dexamethasone is reported. In sum, Kyle does not direct the skilled person to use a combination of thalidomide with dexamethasone in the treatment of multiple myeloma over thalidomide.

The PTO recognizes that Kyle does not teach the use of pomalidomide for treating multiple myeloma (Page 3 of the Action). Indeed, Kyle does not mention pomalidomide, much less its use in treating multiple myeloma that is relapsed or refractory to thalidomide or other previous therapy.

Furthermore, Kyle does not disclose or suggest the doses recited in the instant claims (1 to 4 mg/day). Kyle discloses that thalidomide was given at a dose of 200 mg/d for two weeks and then increased as tolerated by 200 mg/d every two weeks to a maximum dose of 800 mg/d (page 585). The doses used in Kyle are much higher than those recited in the instant claims. Thus, even if Kyle motivated one to select pomalidomide, and it does

not, Kyle teaches away from the claimed dosage range. Prior art is said to teach away from a claimed invention "[w]hen a piece of prior art 'suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant....'" *Medichem*, 437 F.3d at 1165 (quoting In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994)) (emphasis added); See also *KSR*, 127 S.Ct. at 1740 (citing United States v. Adams, 383 U.S. 39, 40 (1966)); MPEP § 2145 (citing *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983)).

Thus, Kyle clearly teaches away (1) from the selection of the recited compound for use in the method, (2) from combining it with dexamethasone, and (3) from using the doses recited by the claims. The PTO improperly ignores all these facts and fails to recognize such facts teach away from the claimed invention in several material respects. Any one of these would be sufficient alone to rebut a *prima facie* case of obviousness based upon Kyle. *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003).

Next, the Office's reliance on Davies does not cure the defects of Kyle. First, Davies explicitly states that the rational for the use of thalidomide in multiple myeloma was anti-angiogenesis. See Davies, page 210, abstract ("The angiogenic activity of thalidomide, coupled with an increase in bone marrow angiogenesis in multiple myeloma, provided the rational for the use of thalidomide in multiple myeloma"). The PTO has simply failed to provide any references that suggest the use of the recited compound as an anti-angiogenesis agent like thalidomide.

Moreover, irrespective of mechanisms, there is no suggestion in the cited art that pomalidomide is effective to treat multiple myeloma, and no suggestion to combine it with dexamethasone. The Office admits that Davies does not teach pomalidomide (page 4 of the Action). Davies merely discloses that the compounds studied are thalidomide, and 3 other IMiDs® or immunomodulatory compounds (IMiD1, IMiD2 and IMiD3). See, page 212. Without identifying thalidomide analogs by their chemical structures or chemical names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds.

In fact, Celgene Corporation, the assignee of this application, used the general terms to designate different compounds at different times in different publications, in order not to reveal the structures of any specific IMiDs® compounds. For example, as evidenced by the references submitted with IDS in this application, while IMiD3 is used to designate methyl-substituted thalidomide in Marriott *et al.* (C 138, page 182), it is used to designate different compound α-3-aminophthalimido-glutarimide in Tsenova *et al.* (C 176, page 1889).

In addition, Davies does not teach or suggest that pomalidomide is more effective than thalidomide in the treatment of multiple myeloma. There would be no basis in Davies to select one compound over the other. Thus, Davies would not lead one skilled in the art to select pomalidomide.

Further, the PTO cannot rely on Corral, because Corral does not cure deficiency of Kyle or Davies. Corral describes differential cytokine modulation and T cell activation by two classes of thalidomide analogues having TNF-α inhibitory activity. Corral concludes that the compounds will be used as investigational tools in animal disease models to define mechanism of pathogenesis and to continue to elucidate the mechanism of action of thalidomide (page 385, first column, last paragraph). However, Corral does not suggest that any compounds disclosed therein can be used for treating multiple myeloma. Moreover, Corral does not even suggest the specific methods for treating multiple myeloma using pomalidomide, much less specific amounts of about 1 to 4 mg/day, or the combination therapy with dexamethasone as claimed.

As to Muller, this reference does not teach treating multiple myeloma. The claimed methods require treating specific multiple myeloma with the specific amounts (1 to 4 mg/day) of pomalidomide and dexamethasone by specific dosing regimens. Applicant points out that the PTO has not borne the burden of establishing *prima facie* obviousness against the claims as a whole.

Further, the PTO has provided no specific source of motivation to combine the teachings of the four references in the particular claimed manner. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Even if the cited references were combined as the PTO alleges, the combination would not have provided the requisite expectation of success. Such is required to establish a *prima facie* case of obviousness. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1090 (Fed. Cir. 2008). When the cited references are combined, one skilled in the art is merely taught that thalidomide may be used for treating multiple myeloma or that certain unidentified immunomodulatory compounds can be explored further. However, the combination of the references would not have provided any indication to use specific amounts (1 to 4 mg/day) of the recited compound in combination with dexamethasone for treating specific multiple myeloma by specific dosing regimens. Because the Office has not demonstrated such, the claimed invention is not obvious by the combination of the cited references.

Nonetheless, the PTO contends that it would be obvious to adjust the amount of the drug depending on its efficacy and side effects as disclosed in Kyle for thalidomide (page 584). (Page 6 of the Action). Applicant respectfully disagrees.

Contrary to the PTO, MacNeil (2010) establishes that the claimed dose is not suggested or obvious by the cited art. Applicant submitted a copy of MacNeil as Exhibit 1 in the response filed on December 23, 2010. MacNeil describes that "small differences in structure of pomalidomide from thalidomide mean very important differences in terms of side effect profiles, efficacy, and potency."

A skilled artisan would have no reason to use the specific claimed dose (1-4 mg/d) of the instant compound (pomalidomide) from the cited art. The Office Action has not pointed to any reason that would have prompted a person skilled in the art to select specific amounts of the recited compound for treating relapsed or refractory multiple myeloma as claimed.

In view of the foregoing, a *prima facie* case of obviousness has not been established, and the rejection under 35 U.S.C. § 103(a) must be withdrawn.

The rejection over the combination of Kyle, Davies, Corral, Muller and 554 Patent

Claims 24-28, 36 and 53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kyle, in view of Davies, Corral, Muller and U.S. Pat. No. 6,555,554. ("554 Patent"). (Pages 6-7 of the Action). Applicant respectfully traverses the rejection.

The Office alleges that the '554 patent discloses a composition comprising pomalidomide, its salt or enantiomers to reduce TNF-α and to improve oncogenic or cancerous conditions, that the composition can be in the form of a tablet or capsule, and that the excipient such as microcrystalline may be added to the composition. Page 7 of the Action. Thus, the Office alleges that it would have been obvious to one of ordinary skill in the art to treat MM by administering pomalidomide in a tablet or capsule containing an excipient such as microcrystalline cellulose. Page 7 of the Action. Applicant disagrees.

The deficiencies of Kyle, Davies, Corral and Muller have been discussed above. The '554 Patent does not cure the lack of teaching or suggestion for the claimed methods. The Office alleges that the '554 Patent discloses methods of reducing TNF-α, or improving oncogenic or cancerous conditions, and a composition containing pomalidomide. (Page 7 of the Action). Applicant does not dispute this disclosure. However, without using improper hindsight, the '554 Patent does not cure the deficiency of Kyle, Davies, Corral and Muller. As the record shows not all TNF-α inhibitors work in treating multiple myeloma,

and many elements of the claimed method are simply missing from even a combination of the five cited references.[1] The law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, at 1379 (Fed. Cir. 2006). The Examiner has provided no specific source of motivation to combine the teachings of the five references for the claimed methods.

Therefore, a *prima facie* case of obviousness has not been established. Applicant respectfully requests that the rejection be withdrawn.

Unexpected Results Support the Nonobviousness of the Instant Claims

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, Applicant submits evidence of unexpected results of the claimed method sufficient to rebut a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); and *Procter & Gamble v. Teva*, 566 F.3d 989 (Fed. Cir. 2009).

The Examiner is required to consider all rebuttal evidence including unexpected results submitted by Applicant. *See In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007), citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007); MPEP §2145. This requirement remains unchanged following the decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), as the Federal Circuit has made clear in *In re Sullivan*. 498 F.3d at 1351.

In the responses filed on December 23, 2010, Applicant submitted several publications, which support that the claimed combination therapy showed surprising and unexpected effects for treating multiple myeloma patients.

In addition, Applicant respectfully invites the Examiner's attention to Schey *et al.*, *Expert Opinion*, 2011 (Exhibit 1); and Lacy *et al.*, *Blood*, 2011 (Exhibit 2), copies of which are submitted herewith. Schey *et al.* discuss several clinical studies with pomalidomide plus dexamethasone combination therapy in multiple myeloma patients who were relapsed

[1] The mere need to use five references to arrive at the claimed invention is an indication of its lack of obviousness.

or refractory to pretreatment with thalidomide, lenalidomide or bortezomib. See pages 695-697 and Table 1.

Kyle that the PTO relied on noted that thalidomide/dexamethasone therapy was found to have significant toxicities. (Kyle, page 586, column 1, lines 13-15). By contrast, the claimed pomalidomide/dexamethasone therapy exhibits surprisingly fewer toxicities. Schey *et al.* describe that the regimen has significant activity in relapsed or refractory multiple myeloma, and that manageable toxicity and the ease of use would provide a valuable agent for relapsed or refractory disease to induce remission and maintenance agent to improve durability of response. See page 697. Schey *et al.* disclose that the low incidence of significant nonhematological toxicity with pomalidomide regimen means that the drug is well tolerated and can be used over prolonged periods. See page 698.

Further, Lacy *et al.* disclose clinical studies where multiple myeloma patients were administered with pomalidomide in combination with dexamethasone. *See* Exhibits 2. Their results showed that the pomalidomide/ dexamethasone regimen is significantly active in refractory myeloma. Lacy *et al.*, at page 2973. The authors reported that their results are important, because myeloma patients that are refractory to pretreatment with thalidomide, lenalidomide or bortezomib have a poor prognosis. *Id.*

The authors stated that the data in their study confirmed remarkable activity of pomalidomide/ dexamethasone regimen in patients who were refractory to other agents. Lacy *et al.*, at page 2975. The authors reported that the responses were durable, and the overall survival rates of 67% and 78% at 6 months are far superior to what would be expected for myeloma patients at the advanced stage. *Id.* The authors concluded that pomalidomide will be a significant drug, covering unmet clinical need in the treatment of relapsed/refractory multiple myeloma. *Id.*

These publications clearly demonstrate unexpected results of the claimed therapy for relapsed or refractory multiple myeloma. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *In re Sullivan*. 498 F.3d at 1351. Applicant respectfully submits that these results are sufficient to rebut any presumption of obviousness that may have been established by the references cited in the Office Action. Thus, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

III. Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: December 20, 2011

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EXHIBIT 1

Expert Opinion

1. Introduction
2. Multiple myeloma
3. Pomalidomide
4. Pomalidomide - clinical trials in myeloma
5. Conclusion
6. Expert opinion

Pomalidomide therapy for myeloma

Stephen Schey[†] & Karthik Ramasamy
[†]*Kings College Hospital Foundation NHS Trust, Denmark Hill, London, UK*

Introduction: The Office of National Statistics (London, UK) has reported 4040 new patients in the year 2007, with an annual age standardized incidence rate of 4.8 per 100,000 population (range 4.7 – 5.0). Overall survival (OS) in the last decade has improved from 2 – 3 years to 7 – 8 years in the UK. The introduction of IMids for the treatment of myeloma has had a significant impact on outcomes in this life-threatening disease.
Areas covered: Pomalidomide, a thalidomide analogue, is a promising anti-myeloma agent with encouraging responses in relapsed/refractory myeloma patients. Pomalidomide has a potent anti-myeloma activity *in vitro* and *in vivo*, acting both directly on myeloma cells and on the cells in the bone marrow microenvironment. We have reviewed the chemistry and mechanisms of action of pomalidomide and the literature on pre-clinical and early Phase I and II clinical trials that demonstrates significant clinical efficacy in the relapsed setting and in lenalidomide refractory myeloma patients.
Expert opinion: Pomalidomide has shown significant activity in relapsed/refractory disease and is now being taken into Phase III trials in combination with dexamethasone. The exact place of pomalidomide in the management of myeloma, however, is evolving as more clinical experience is gained with this agent and further data published from clinical trials.

Keywords: IMiD, immunomodulation, myeloma, pomalidomide

Expert Opin. Investig. Drugs (2011) 20(5):691-700

1. Introduction

Pomalidomide (CC-4047; 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; **Box 1**), is a novel immunomodulatory drug initially developed for the treatment of multiple myeloma (MM) and used more recently in the treatment of myelofibrosis. Thalidomide, following initial teratogenic reports [1,2], was withdrawn in the 1960s and subsequently revived for clinical use in lepra reactions [3]. Identification of its immunomodulatory [4], anti-inflammatory [5] and antiangiogenic [6] effects were resulted in the development of analogues with enhanced activity and less toxicity, ultimately leading to the development initially of lenalidomide (CC-5013) and later pomalidomide.

2. Multiple myeloma

Myeloma was first described by Solly [7] in 1844, but more than 100 years elapsed before effective treatment became available in the form of melphalan [8]. Combination chemotherapy improved outcomes for younger patients, but until recently melphalan and prednisolone remained the most effective treatment for patients aged > 65 years [8,9]. All patients will ultimately relapse and finally will become refractory to all agents including melphalan, bortezomib and lenalidomide. Myeloma is a heterogeneous disease with variable genetic, phenotypic and clinical features. Better classification of hematological malignancies has made it possible to identify

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Box 1. Drug summary.

Drug name (generic)	Pomalidomide
Phase (for indication under discussion)	Phases I and II
Indication (specific to discussion)	Myeloma
Pharmacology description/ mechanism of action	Immunomodulatory drug
Route of administration	ORAL
Chemical structure	4-amino-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione - please see **Figure 1B**
Pivotal trial(s)	[12,35,56,60]

differences in disease characteristics and patient phenotype that facilitate a risk-adapted treatment approach to maximize anti-myeloma activity while reducing toxicity.

In a retrospective analysis of newly diagnosed myeloma patients, the median overall survival (OS) between 1996 and 2006 was 44.8 months compared to 29.9 months in patients diagnosed between 1971 and 1996 ($p \leq 0.001$) [10]. Epidemiological studies show improved median 10-year survival in the 10 years leading up to the beginning of the 21st century. In a study from Sweden [11], 10-year relative survival rates (RSRs) improved significantly ($p < 001$) in patients < 60 years at diagnosis with a 29% lower 10-year excess mortality among patients diagnosed between 1994 and 2003 versus those diagnosed between 1987 and 1993. In a similar study by Brenner *et al.* [12], 5-year and 10-year RSRs showed a similar increase from 28.8 and 11.1% between 1990 and 1992 to 56.7 and 41.3%, in the age group 50 years or less and to 48.2 and 8.6% in the age group 50 to 59 years between 2000 and 2004. Only moderate improvement was seen in the age group 60 to 69 years, and essentially no improvement among older patients.

2.1 Treatment of relapsed/refractory multiple myeloma

Treatment options for primary resistant or relapsed MM include combination therapies of glucocorticoids and cytotoxic chemotherapeutic agents [13-15] and autologous stem cell transplantation (ASCT) [16,17].

2.1.1 *Dexamethasone*

Dexamethasone, a synthetic adrenal corticosteroid, used alone or in combination with other agents, has been used for relapsed MM as the comparator in several relapsed/refractory and newly diagnosed myeloma studies [18]. Responses range from 18 to 28% [18,19] in large Phase III trials, and it is particularly useful in patients with renal impairment or myelosuppression.

2.1.2 *Lenalidomide*

Lenalidomide in combination with dexamethasone is approved in the United States and Europe for the treatment of patients with MM who have received at least one prior therapy. This combination is associated with the overall response rates (ORRs) ranging from 43 to 82%, depending on the number and type of prior therapies [20,21].

2.1.3 *Bortezomib*

Bortezomib monotherapy is approved in the EU for the treatment of patients with MM who have received at least one prior treatment and have already undergone or are unsuitable for bone marrow transplantation [18]. It is also approved in combination with melphalan and prednisone is in the United States and Canada for the treatment of patients with relapsed or previously untreated MM and is currently being appraised by NICE (National Institute for Clinical Excellence) in the UK. In combination with pegylated liposomal doxorubicin, it is approved in the United States for patients who have not previously received bortezomib and have received at least one prior therapy [22].

Experimental treatment regimens of 3 and 4 licensed drug combinations with alkylating agents, steroids and each other are being evaluated in the setting of relapsed/refractory disease [23]. Other combinations with (liposomal) doxorubicin bendamustine and with histone deacetylase (HDACs) inhibitors and heat shock protein (HSP) inhibitors are underway in an attempt to enhance their activity and overcome resistance.

The second-generation proteasome inhibitor, carfilzomib has been shown to be safe and effective for patients failing to respond to velcade [24]. Ongoing studies are evaluating carfilzomib in velcade-naive patients [25] and in combination with lenalidomide and dexamethasone [26]. Bendamustine is a bifunctional purine analogue/alkylaytor, containing a chloroethylamine alkylating group, a butyric acid side chain and a unique purine and amino acid antagonist benzimidazole ring. It is licensed by the EMEA (European Medicines Agency) for myeloma in combination with prednisone for patients older than 65 years who are not eligible for ASCT and cannot be treated with thalidomide or bortezomib. Studies assessing the impact of combination therapies in the relapsed/refractory setting are ongoing.

The most appropriate salvage regimen in an individual patient is dependent upon the initial therapy regimen, the depth and duration of response to that therapy, toxicity of the treatment, patient comorbidities and the treatment options in that individual [27]. Treatment options include rechallenge of a previous chemotherapy regimen provided 6 – 12 months has elapsed since last therapy or a trial of a new chemotherapy regimen. Until recently, the median survival following relapse after induction therapy was approximately 1 year [28].

3. Pomalidomide

Thalidomide, the parent compound, is a synthetic glutamic acid derivative (**Figure 1** Panel A) [29]. Pomalidomide is a thalidomide analogue with an additional amino group in the fourth carbon of the pthaloyl ring. Pomalidomide differs from

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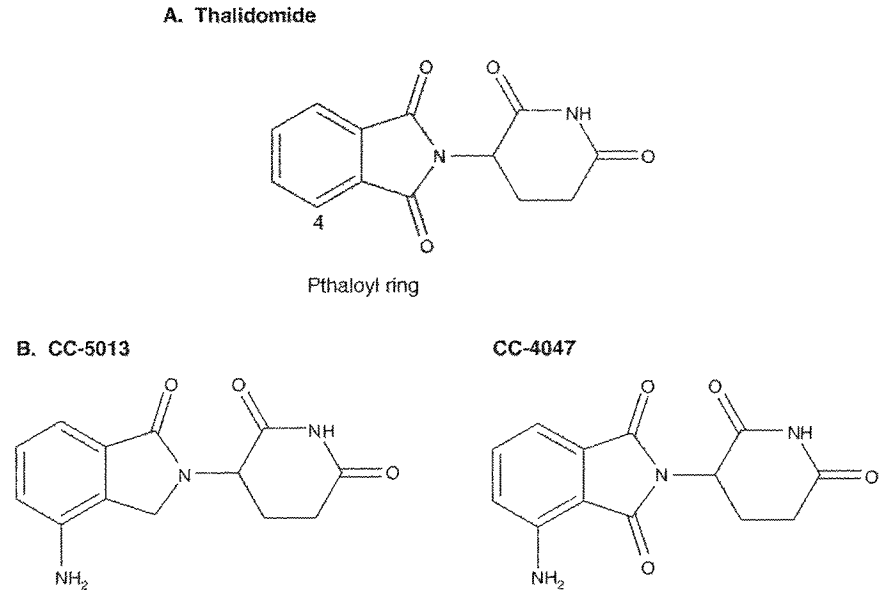

Figure 1. Chemical structure of thalidomide and its analogues. A. Thalidomide with pthaloyl ring, part of its chemical structure modified in the analogues highlighted in gray. **B.** Chemical structure of CC-4047, pomalidomide with additional amino group and CC-5013, lenalidomide with additional amino group but missing carbonyl group in the pthaloyl ring.
Adapted with permission from [29].

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lenalidomide in its chemical structure by having an additional carbonyl group in the pthaloyl ring (**Figure 1** Panel **B**).

3.1 Immunomodulatory activity

Myeloma patients have a defective immune response and immune surveillance. Studies of antigen-processing machinery in myeloma patients show reduction in expression of proteasome subunits and peptide transporters at the transcriptional level. These results allude to antigen-processing aberration as one of the mechanisms of impaired immune surveillance in myeloma patients [30]. Cancer testis antigens are aberrantly expressed by myeloma cells and are a potential immunotherapeutic target. CD4+ T cell immunity and cytotoxicity against MAGE (melanoma antigen gene)-positive myeloma cell lines was observed more in monoclonal gammopathy of undetermined significance (monoclonal gammopathy of uncertain significance; MGUS) than MM patients, suggesting that once the patients progress, they lose their ability to mount a T-cell response. $CD8^+$ memory T cell response was seen exclusively in myeloma patients but was poorly recruited into the bone marrow [31]. Increased frequency of naturally occurring functional CD4(+)CD25(+)FoxP3(+) T cells called T regulatory cells (Tregs) is reported in patients with myeloma as well as MGUS, in comparison with age-matched, healthy control. But their role in disease progression remain unclear [32]. Expression of MIC-A and NKG2D in myeloma patients were lower in comparison to MGUS patients and could potentially be linked to disease progression [33]. Defective B7:CD28 costimulation has also been described in myeloma patients [34].

Pomalidomide has T cell costimulatory activity, thereby enhancing durable, antigen-specific Th1 type response *in vivo* [35]. In a colon cancer murine model, mice challenged with tumor cells, not expressing the costimulatory molecule with pomalidomide, showed enhanced production of IL-2 and IFN-γ. This response continued to last for 2 further rounds of live tumor challenges [35]. NK and NK T cell populations were increased when prostate cancer, myeloid and lymphoid cancer cell lines were cocultured in the presence of pomalidomide with peripheral blood mononuclear cells (PBMCs) of patients. Pomalidomide dose dependently induced NK-mediated tumor cell apoptosis [36] in these cocultures and in myeloma cell lines *in vitro* [37]. Pomalidomide and lenalidomide also suppress T-reg cell function and proliferation. Treatment with pomalidomide decreased T-reg numbers in mice, although no direct cytotoxicity was demonstrated *in vitro*. Pomalidomide decreased IL-2-mediated generation of T-reg cells from PBMCs by half and inhibited T regulatory cell function. The reduction in function was not mediated by TGF-β or IL-10 production (**Figure 2**) [38].

3.2 Angiogenesis

Angiogenesis in myeloma bone marrow is mediated by plasma cells, stromal cells and endothelial cells in the microenvironment. Bone marrow biopsies from MGUS and early and advanced myeloma were stained with factor VIII (FVIII) antigen, showing significantly increased microvascular density in relapsed myeloma [39]. VEGF secreted by plasma cells acts on cognate receptors on stromal cells releasing soluble factors

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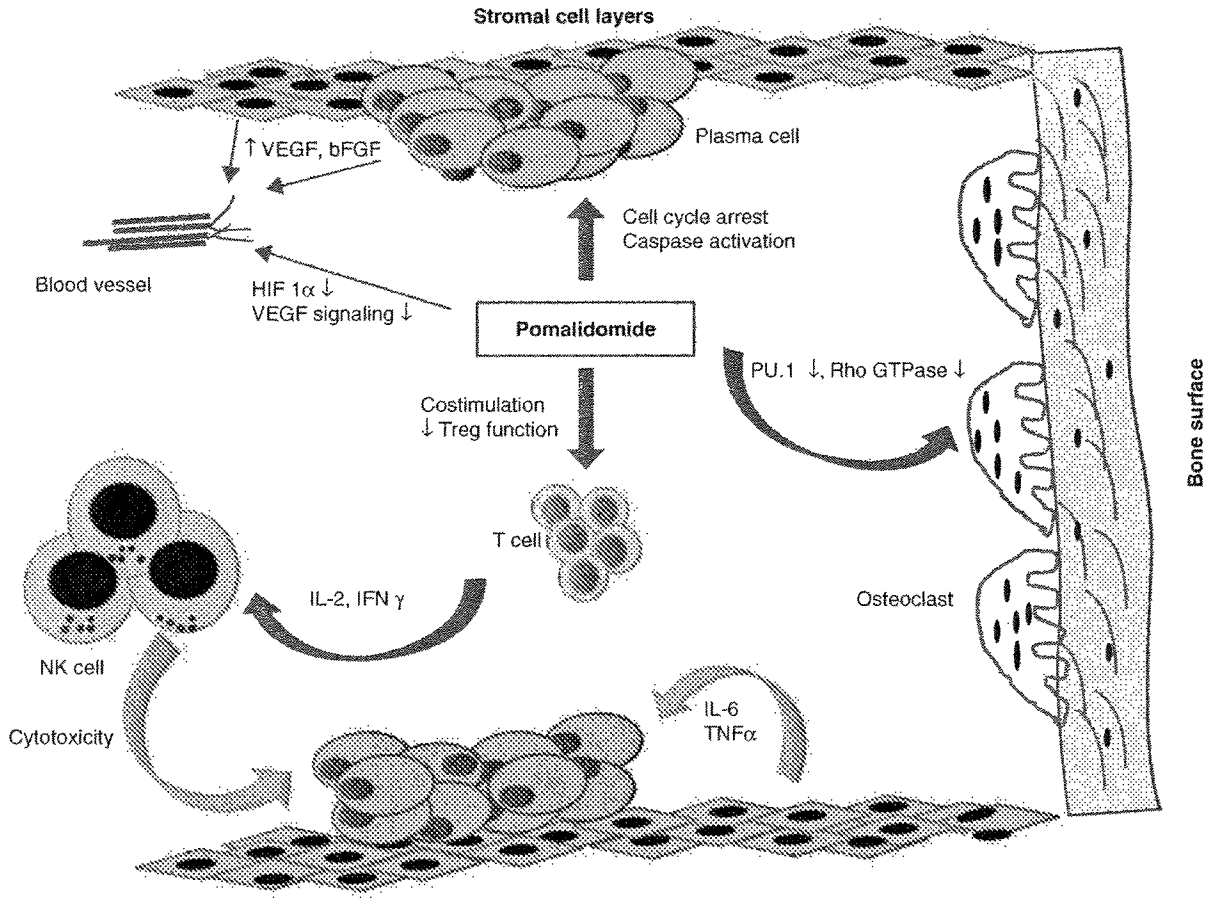

Figure 2. Pomalidomide and its effects on the plasma cells and the microenvironment.

that drive plasma cell proliferation in a paracrine manner (Figure 2) [40]. Thalidomide also possesses antiangiogenic properties that significantly reduced microvascular density in bone marrows of responding myeloma patients, with no reduction in angiogenesis in nonresponders [41]. Treatment with pomalidomide in SCID mice carrying lymphoma tumors from Raji cell line, significantly inhibited angiogenesis as evidenced by decreased CD31 staining in the tumors, as compared to placebo controls [42]. Pomalidomide showed greater inhibition of endothelial sprout formation in a human umbilical artery explant assay compared to lenalidomide and blocked VEGF-induced endothelial cell cord formation in hypoxic and normoxic conditions (Figure 2). In hypoxic conditions, hypoxia inducible factor (HIF) proteins enhance angiogenesis. In hypoxic conditions, pomalidomide downregulated HIF-1α but not HIF-2α in endothelial cell cultures [43].

3.3 Direct anti-myeloma activity

Pomalidomide has significant anti-myeloma activity *in vitro* and *in vivo*. Pomalidomide causes cell cycle arrest in plasma cells by p21 WAF activation which is p53 independent [44]. Pomalidomide induces plasma cell apoptosis by inducing caspase 8 activation and downregulating the NFkB pathway which is universally activated in myeloma cells [45]. The enhanced antitumor responses in combination with dexamethasone are explained by the fact that dexamethasone activates caspase 3 that synergizes with apoptotic cell death induced by pomalidomide [46]. Pomalidomide apart from direct proapoptotic activity inhibits adhesion to stromal cells and secretion of cytokines such as IL-6, thereby promoting tumor cell death [47].

3.4 Bone disease

Skeletal abnormalities are observed in up to 90% of patients with myeloma during the course of their disease [48]. In a population-based retrospective cohort study, 16 times more fractures, mostly of the vertebrae and ribs, were observed than expected in the year before diagnosis. Patients with a pathological fracture had poor survival [49]. Pomalidomide inhibits lineage commitment required for early differentiation of osteoclasts under the influence of cytokines due to the downregulation of PU.1 resulting in the inhibition of osteoclast production and function [50]. The lack of differentiation completely inhibited

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bone resorption. Osteoclasts are motile dynamic cells switching from resorptive to non-resorptive phases, depending on the surface that they are cultured on. This phenotypic switch is dependent on the regulation of the actin cytoskeleton. Pomalidomide-modulated Rho GTPases affecting actin cytoskeleton in osteoclasts results in increased cell migration and lack of bone resorption [51].

3.5 Anti-inflammatory property

Pomalidomide is a potent anti-inflammatory agents. Pomalidomide, significantly decreased TNF-α production by lipopolysaccharide (LPS)-induced monocyte activation *in vitro*, and endotoxic shock when delivered in large doses *in vivo* [52]. Cyclooxygenase-2 (COX-2) is highly expressed in myeloma patients and is associated with a poor outcome [53]. A dose-escalating trial of celecoxib administered with thalidomide showed an improved progression free and OS with higher dose of COX-2 inhibitor [54]. Pomalidomide also inhibits COX-2 production reducing COX-2 levels and production of prostaglandins in human LPS-stimulated monocytes. The inhibition of COX-2 occurs at the level of gene transcription, by reducing the LPS-stimulated transcriptional activity at the *COX-2* gene [55]. Because of this specific activity, the toxic side effects observed with other COX-2 inhibitors can be safely avoided.

4. Pomalidomide - clinical trials in myeloma

Pomalidomide has undergone extensive preclinical testing, but clinical experience in relapsed and/or refractory MM is limited (**Table 1**).

4.1 Relapsed myeloma

4.1.1 Phase Ib study (CDC-407 – 00-001/ CC-4047-MM-001)

This was a Phase Ib, first in man, single-center, dose-escalation (1, 2, 5 and 10 mg), open-label study of pomalidomide given continuously [56] (cohort 1) or on alternate days [57] (cohort 2) to a total of 45 subjects relapsing or considered refractory to treatment after at least two cycles of treatment. Patients were excluded an absolute nucleated cell count (ANC) > 1000, platelets 20,000 and a serum creatinine < 200 µmol/l. The median age in Cohorts 1 and 2 was 58 years and 66 years, respectively (range 49 – 82), and the median number of prior regimens was 3 (range 1 – 6) and 4 (range 1 – 7), respectively. Of the 45 patients, 18 (40%) had previously received an autologous stem cell transplant and 24 (53%) had received prior thalidomide therapy.

Median time to reach maximum serum concentration (t_{max}) was 2.5 – 2.75 h, while the mean half-life ($t_{1/2}$) was 6 – 8 h. Two-thirds of the drug is excreted in the urine and there was minimal accumulation by day 28 of administration. The maximum tolerated dose (MTD) was 2 mg continuously and 5 mg on alternate days. The most common dose-limiting toxicity (DLT) was grade 4 neutropenia but no grade 3/4 neutropenia occurred on cycle 4 or later, no patients required growth factor support and no neutropenic sepsis was observed. The most common adverse events (AEs) were neutropenia (58% G3/4), thrombocytopenia, cough, dyspnea and lethargy. National Cancer Institute Clinical Toxicity Criteria (NCI CTC) grade 1 – 2 nonhematological toxicity was reported in 2 patients (8%) who experienced a deep vein thrombosis (DVT; grade 3) at 5 and 8 months, respectively. One further patient developed a DVT at 3 weeks, but this was secondary to inguinal lymphadenopathy on the same side as the thrombus secondary to an undiagnosed melanoma at the time of study entry, giving an overall incidence of 12.5%. No DVTs were experienced in the alternate day Cohort 2 group. There were three cases of grade 1 neuropathy, not necessitating discontinuation from study; all cases resolved without further intervention. Overall, 23 (51%) of 45 subjects had partial response (PR) or better including 6 (13%) complete response (CR) and 12 (27%) very good partial response (VGPR). Progression free survival (PFS) and OS was 9.75 and 22.5 months and 10.5 months and 35.9 months in Cohorts 1 and 2, respectively.

4.1.2 Celgene-initiated Phase Ib/II study (CC-4047-MM-002)

A Phase I/IIb multicenter, randomized, open-label, dose-escalation (2, 3, 4 and 5 mg) study is evaluating the MTD and the safety and efficacy of pomalidomide alone using a cyclic regimen (21 of 28 days) and in combination with low-dose dexamethasone in subjects who have received ≥ 2 prior regimens and do not achieve at least a partial response to bortezomib and lenalidomide [58]. Thirty-eight subjects have been enrolled in Phase I cohort. The MTD was 4 mg which is the dose selected for the Phase II cohort. The safety profile was similar across cohorts except for grade 4 neutropenia, which increased in the 5 mg cohort. In 26 evaluable subjects, minimal response (MR) or better was reported in 17 subjects (65%) including 1 CR and 6 PR. As of September 22, 2010, 221 subjects have been enrolled in the Phase II segment.

4.1.3 Phase II study (PO-MM-PI-0010)

This was a Phase II open-label study of pomalidomide (2 mg continuous) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15 and 22) in subjects with relapsed/refractory MM who had received 1 – 3 prior regimens [59]. Pomalidomide was given as 2 mg/day orally on days 1 – 28 with dexamethasone 40 mg p.o. on days 1, 8, 15 and 22 (Cohort 1). Patients were allowed to increase to the dose to 4 mg/day if nonresponding or progressing, provided there was no grade 3/4 toxicity (Cohort 2). Patients received aspirin 325 mg/day for thromboprophylaxis. A total of 60 subjects were enrolled. The most common grade 3/4 hematological toxicity was neutropenia reported in 21 patients (35%) and the most common nonhematological grade 3/4 toxicities were fatigue and pneumonia. Thirty-eight (63%) of the 60 subjects responded, including 3 (5%) CR, 17 (28%) VGPR and 18 (30%) PR.

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Table 1. Pomalidomide clinical trials.

Trial	Number of participants	Drugs	Specific inclusion criteria	Response	Remarks
Phase Ib Study (CDC-407-00-001/ CC-4047-MM-001), open-label dose-escalation study	45	Pomalidomide	Relapsed/ refractory	51% > PR	MTD – 2 mg daily or 5 mg alt days
Celgene-Initiated Phase Ib/II Study (CC-4047-MM-002):	221	Pomalidomide (21/28 days) + Dex	> 2 lines of therapy and < PR to thalidomide and bortezomib	ORR 65% in Phase Ib (evaluable patients)	MTD – 4 mg, used in Phase II cohort
Phase II study (PO-MM-PI-0010)	60	Pomalidomide (2 mg continuous) + Dex weekly	Relapsed/ refractory	ORR 63%	Responses seen in Len, Bort and Thal refractory patients
Phase II study (Mayo)	34	Pomalidomide (2 mg continuous) + Dex weekly	Lenalidomide refractory	ORR 47%	41% high-risk disease, median PFS 4.8 months
Randomized Phase II study (IFM 2009-02) IFM group	84	Pomalidomide (4 mg continuous) vs Pomalidomide (21/28 days) + Low dose Dex	Patients resistant or refractory to lenalidomide and bortezomib	ORR 47 vs 30%	All patients had high-risk cytogenetics
Mayo study in double-refractory myeloma	70	Pom (2 mg continuous) + 40 mg Dex weekly vs Pom 4 mg continuous + 40 mg Dex weekly	Patients resistant or refractory to lenalidomide and bortezomib	ORR 49 vs 40%	4 mg/day pomalidomide not superior to 2 mg/day of pomalidomide in combination with dex

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A total of 82% of patients who remained on treatment for a minimum of 12 weeks demonstrated a 25% or greater decrease in measurable paraprotein. Responses were seen in 8 (40%) of 20 lenalidomide-refractory subjects, 6 (37%) of 16 thalidomide-refractory subjects, and 6 (60%) of 10 bortezomib-refractory subjects, suggesting noncross resistance between these agents. Five patients had previously received and were refractory to both bortezomib and lenalidomide, of whom 2 had a PR and 1 a VGPR. In all, 19 patients were considered high risk with adverse cytogenetics or a high plasma cell-labeling index of whom, 14 (74%) had responses including 1 (5%) CR, 5 (26%) VGPRs and 8 (42%) PRs. Five patients had deletion of chromosome 17p, 3 (60%) VGPR and 2 (40%) PR. At 6 months, 97% of responders continued to respond and 94% of patients were alive; median PFS was 11.6 months and that in the poor risk group is comparable to that seen in standard risk disease which is encouraging.

The different response rates reported between the studies may be related to the differing entry criteria; patients had a median of 4 prior lines of therapy in the IFM study, while it was 6 in the Mayo study.

4.2 Lenalidomide-refractory myeloma

The Mayo group conducted a further single-stage, Phase II study of patients shown to be refractory to previous treatment with lenalidomide [60]. Lenalidomide refractoriness was defined as relapsing on or within 60 days of stopping lenalidomide. In all, 34 patients were entered into the study. Subjects received pomalidomide at a dose of 2 mg/day on days 1 – 28 of a 28-day cycle. Dexamethasone was given at a dose of 40 mg/day on days 1, 8, 15 and 22 of each cycle. Patients received aspirin 325 mg for thromboprophylaxis. The median age was 62 years (range: 39 – 77). The median number of previous regimens was 4. Twenty-eight, 37 and 35% of the patients had 1, 2 and 3 previous regimens, respectively, while 68% had received a previous autologous stem cell transplant and 1 patient had received both an autologous and an allogeneic stem cell transplant. All patients had previous lenalidomide therapy; 19 (58%) previous thalidomide and 20 (59%) previous bortezomib. Preexisting baseline peripheral neuropathy was present in 20 patients (59%). Fourteen (41%) were classified as high risk. Median follow-up is 8.3 months. VGPR was seen in 3 (9%), PR in 8 (23%) and MR in 5 (15%) patients, giving an ORR of 47%. Twelve (35%) patients had stable disease. The median time to response is 2 months (range: 0.7 – 3.9). Of the 14, 8 (57%) high-risk patients responded; 4 (14%) PR and 4 (14%) MR. Responses were seen in 8 (42%) of 19 patients who received previous thalidomide and 9 (45%) of the 20 patients who had previous bortezomib. The dose of pomalidomide was increased from 2 to 4 mg/day in 8 patients; only 1 patient improved their response from SD to PR. The median

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duration of response in the 11 patients achieving PR or greater was 9.1 months. The median PFS was 4.8 months, and this was not significantly different in the high-risk disease compared with those with standard risk disease. The median OS time is 13.9 months for all the patients.

4.3 Lenalidomide- and bortezomib-resistant disease

4.3.1 Investigator-initiated Phase II study (IFM 2009-02; ongoing)

This is a multicenter, randomized Phase II, open-label study of pomalidomide plus dexamethasone in 84 subjects with relapsed and refractory MM who have previously received bortezomib and lenalidomide, conducted by Intergroupe Francais du Myelome (IFM). Subjects received a 4-mg dose of pomalidomide, given either as a cyclic (21-day out of 28-day cycles) regimen in combination with low-dose dexamethasone (Arm A) or continuously (28-day) (Arm B). The primary end point was response rate and the secondary end points were safety, time to response, time to disease progression and OS. At the 2010 American Society of Haematology (ASH) meeting, 83 subjects had been entered, all of whom had poor risk cytogenetics (loss of 17p and/or t (4:14) translocation). In Arm A, 30% of patients achieved a PR or greater (1 VGPR), while in Arm B 47% had a PR or greater (1 VGPR). Median duration of response was 77 and 89 days, respectively, with a median follow-up of 119 days. The drug was well tolerated, with no thromboembolic or neuropathy complications reported [61].

4.3.2 Investigator-initiated study comparing 2 dosing strategies (Mayo clinic)

Mayo clinic presented a study at ASH 2010 comparing 2 dosing strategies in patients refractory to both lenalidomide and bortezomib. Pomalidomide given orally 2 mg/day (Cohort A) or 4 mg/day (Cohort B) on days 1 – 28 of a 28-day cycle with oral dexamethasone given 40 mg/per on days 1, 8, 15 and 22. All patients received aspirin 325 mg daily for thromboprophylaxis. In all, 35 patients with relapsed and resistant/refractory to both lenalidomide and bortezomib were enrolled in each cohort. The median age was 62 years (range, 39 – 77) in Cohort A and 61 (range, 45 – 77) years in Cohort B. The median duration on treatment was 5(1 – 13) and 2 (0 – 6) cycles in cohorts A and B, respectively. The median follow-up on alive patients was 7.5 months and 3 months in Cohorts A and B, respectively. Toxicity observed was primarily myelosuppression: grade 3/4 neutropaenia (37% Cohort A vs 55% Cohort B); grade 3/4 thrombocytopaenia (11% Cohort A vs 13% Cohort B); and grade 3/4 anemia (9% Cohort A vs 16% Cohort B). Grade 3/4 nonhematologic toxicities occurred in 23% Cohort A vs 13% Cohort B. Hematological responses in Cohort A consisted of VGPR 14%, PR 11% and MR 24% (ORR 49%, 95% CI: 31 – 66), and responses in Cohort B consisted of VGPR 9%, PR 20% and MR 12% (ORR 40%, 95% CI: 23 – 58). The median PFS in Cohorts A and B were 6.4 months (95% CI: 4.7 - no response [NR]) and 3.3 months (95% CI: 2.3 - NR), respectively. This study confirms therapeutic benefit for Pom/dex in patients relapsing after lenalidomide and bortezomib. This study did not demonstrate an advantage of using a higher dose of pomalidomide 4 mg/day on days 1 – 28 of each 28-day cycle [62].

4.4 Toxicity

Toxicity from pomalidomide is primarily due to myelosuppression. Neutropenia is the commonest complication, but grade 1 and 2 thrombocytopenia and anemia are reported in < 5% of patients. Nonhematological complications are rare and tend to be grade 1 – 2 only. Hypoglycemia, constipation and diarrhea are also reported in < 5% of patients. Throughout the studies, neuropathy either is not reported or occurs in < 5% of patients, and venous thromboembolic disease is not increased above that reported in patients treated with conventional chemotherapy. However, thromboprophylaxis was given in the Phase I and II studies.

4.5 Other combination studies

A Phase III randomized study of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone for patients relapsed after being shown to be refractory to both lenalidomide and bortezomib is being planned to open in 2011 in the UK and Europe.

5. Conclusion

Pomalidomide a new IMiD has significant activity in relapsed/refractory myeloma with potent immunomodulatory effect. Manageable toxicities observed in clinical trials and the ease of use would provide a valuable addition to the increasing list of available agents that can be used for resistant/refractory disease to induce remissions and as a maintenance agent to improve durability of response.

6. Expert opinion

There are an increasing number of patients who are refractory, respond suboptimally or experience significant toxicity to either bortezomib or lenalidomide therapy. Gertz *et al.* in a retrospective analysis reported that patients who never respond or relapse on treatment with a thalidomide- or lenalidomide-containing regimen have a significantly shorter PFS and OS following stem cell transplantation than those who achieve at least a PR [63]. Furthermore, although by combining lenalidomide and bortezomib, up to 100% of *de novo* patients achieved at least a PR, patients continue to relapse and significantly less respond at the time of relapse [64,65]. There remains, therefore, a clinical need for new agents. Pomalidomide has been shown to be effective in overcoming resistance to both bortezomib and lenalidomide. The 40% response rate in lenalidomide-refractory patients reported in early Phase II trials implies non-cross-resistance for pomalidomide, suggesting a role for this drug in the treatment of relapsed patients, supporting the laboratory results observed in lenalidomide-resistant

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cells [66]. Also notable is the high remission rate (74%) seen in patients from a Phase II relapse study [59] with high-risk disease. The median progression-free survival was 11.6 months and was not significantly different in the patients with high-risk disease compared to those with standard risk disease, which supports the use of pomalidomide.

Data is now emerging for thalidomide and lenalidomide that maintenance prolongs both PFS and OS [67-70]. The low incidence of significant nonhematological toxicity with pomalidomide means that the drug is well tolerated and can be given over prolonged periods. This raises the possibility of utilizing pomalidomide as a maintenance agent or perhaps in the treatment of high-risk precursor conditions such as smouldering myeloma [71]. Furthermore, the potent *in-vitro* and *in-vivo* immunomodulatory activity of this agent makes it an ideal candidate to use as an adjuvant for immunotherapeutic strategies such as vaccine therapies for the treatment of myeloma [35,72,73] and other malignancies.

Pomalidomide has also shown activity in upregulating fetal erythropoiesis by causing a switch in lineage commitment [74]. Fetal hemoglobin (HbF) has higher oxygen affinity than normal adult hemoglobin (HbA_2) and could potentially be effective in improving fatigue and lethargy in patients with dysregulated erythropoeisis such as hereditary hemoglobinopathies.

Declaration of interest

The authors declare no conflict of interest and have received no payment in preparation of this manuscript.

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EXHIBIT 2

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Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease

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Pomalidomide at doses of 2 or 4 mg/d has demonstrated excellent activity in patients with multiple myeloma (MM). We opened 2 sequential phase 2 trials using the pomalidomide with weekly dexamethasone (Pom/dex) regimen at differing doses to study the efficacy of this regimen in patients who have failed both lenalidomide and bortezomib. Pomalidomide was given orally 2 or 4 mg daily with dexamethasone 40 mg weekly. Thirty-five patients were enrolled in each cohort. Confirmed responses in the 2-mg cohort consisted of very good partial response (VGPR) in 5 (14%), partial response (PR) in 4 (11%), minor response (MR) in 8 (23%) for an overall response rate of 49%. In the 4-mg cohort, confirmed responses consisted of complete response (CR) in 1 (3%), VGPR in 3 (9%), PR in 6 (17%), MR in 5 (14%) for an overall response rate of 43%. Overall survival at 6 months is 78% and 67% in the 2- and 4-mg cohort, respectively. Myelosuppression was the most common toxicity. This nonrandomized data suggests no advantage for 4 mg over the 2 mg daily. Pomalidomide overcomes resistance in myeloma refractory to both lenalidomide and bortezomib. This trial is registered at http://ClinicalTrials.gov, number NCT00558896. (*Blood*. 2011;118(11): 2970-2975)

Introduction

The introduction of thalidomide was crucial in the treatment of myeloma.[1] Promising clinical results led to the development of a class of thalidomide analogues termed immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide. The availability of novel therapeutic agents has favorably affected the survival of patients with myeloma.[2] Pomalidomide is the newest IMiD, and has single-agent activity in relapsed myeloma.[3,4]

Our earlier studies demonstrated that pomalidomide, 2 mg daily, with weekly dexamethasone (Pom/dex) has excellent activity in relapsed myeloma.[5] Subsequent trials confirmed activity in patients with relapsed disease who were refractory to lenalidomide.[6] Follow-up trials have focused on determining the optimal dosing schedule of this agent to maximize clinical benefit. This led to trials with pomalidomide at doses of 4 mg, either continuously or for 21 of 28 days[7,8] as salvage therapy for patients with heavily pretreated relapsed myeloma.

The goals of this nonrandomized study were to determine whether the Pom/dex regimen was effective in patients refractory to both bortezomib and lenalidomide (dual-refractory myeloma) and to ascertain whether starting with a higher dose (4 mg daily) yields better response rates compared with the lower starting dose (2 mg daily) that we have used in earlier trials. We report on 2 sequential phase 2 trials of Pom/dex that addressed these questions.

Methods

Eligibility

Patients were eligible to enter on the study if they had previously treated, symptomatic multiple myeloma (MM). Patients had to be refractory to lenalidomide and bortezomib therapy. For this purpose, refractory disease was defined as relapse on or within 60 days of stopping treatment. Patients were required to have measurable disease defined by one of the following: serum monoclonal protein > 10 g/L, serum immunoglobulin free light chain (FLC) > 10 mg/dL and an abnormal FLC ratio, urine light chain excretion ≥ 200 mg/24 hours, measurable soft-tissue plasmacytoma that had not been radiated, or $> 30\%$ plasma cells in BM. Patients also needed platelet count $> 75 \times 10^9$/L, absolute neutrophil count $> 1.0 \times 10^9$/L, and creatinine $< 221\,\mu$M (2.5 mg/dL). All previous cancer therapy, including chemotherapy and an investigational agent, must have been discontinued ≥ 2 weeks before study registration. Patients with uncontrolled infection, another active malignancy, deep vein thrombosis that had not been therapeutically anticoagulated, Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4, grade 3 or 4 peripheral neuropathy, pregnant or nursing women, women of childbearing potential who were unwilling to use a dual method of contraception, and men who were unwilling to use a condom were excluded. The study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki.

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Treatment schedule

Pomalidomide was given orally at a dose of 2 or 4 mg daily on days 1-28 of a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, and 22 of each cycle. Patients also received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full-dose anticoagulation with either low-molecular-weight heparin or warfarin at physician discretion. G-CSF was not allowed to avoid dose reductions but could be used if a patient developed neutropenic fever.

Dose adjustments were permitted based on toxicity as described. Pomalidomide was to be permanently discontinued in the event of a grade 4 rash, neuropathy, or hypersensitivity, and grade 3 or higher bradycardia or cardiac arrhythmia. Pomalidomide was progressively reduced for other related grade 3 or higher adverse events to dose levels of 2 or 4 mg for 21 days each 28-day cycle. Subsequently, doses were decreased by 1 mg for the 4-mg cohort until a dose of 2 mg for 21 days of each 28-day cycle was reached. Subsequent doses were decreased by 0.5 mg. When grade 3 or 4 adverse events occurred before day 15 of a cycle and resolved to grade 2 or lower before day 28 of the cycle, pomalidomide was resumed at the next lower dose level, with the next cycle continuing at the reduced dose level. For grade 3 or 4 adverse events occurring on or after day 15 of a given cycle, pomalidomide was held for the remainder of the cycle and reduced by one dose level beginning with the next cycle. Dose reductions were permitted for dexamethasone related toxicity, by lowering the dose of dexamethasone progressively to 20 mg, 12 mg, 8 mg, and 4 mg once weekly. Patients unable to tolerate the lowest doses of pomalidomide or dexamethasone needed to stop therapy with that agent permanently. In the absence of grade 3 or higher toxicity, the daily dose of pomalidomide could be increased at physician discretion to 4 mg in patients who had not achieved a 25% reduction in serum or urine monoclonal protein levels after 2 cycles of therapy or who had previously responded and had rising serum or urine monoclonal protein levels. Among patients who had a previous dose reduction, escalation was allowed as long as there was no current grade 3 or 4 toxicity.

Response and toxicity criteria

Responses were assessed according to published criteria of the International Myeloma Working Group.[9] A partial response (PR) was defined as $\geq$ 50% reduction in the level of the serum monoclonal (M) protein and/or a reduction in 24-hour urinary light chain excretion $\geq$ 90% or to $<$ 200 mg or as $\geq$ 50% reduction in BM plasma cells, if BM was the only measurable parameter at baseline, and baseline percentage was $\geq$ 30%. In addition to the these criteria, if a plasmacytoma was present at baseline, $\geq$ 50% reduction in the size of soft-tissue plasmacytomas was also required. Minor response (MR) was defined as $\geq$ 25% but $<$ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50%-89%, which still exceeds 200 mg per 24 hours In addition, if a plasmacytoma was present at baseline 25%-49% reduction in the size of soft tissue plasmacytomas was also required.

Complete response (CR) required complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and $<$ 5% plasma cells on BM examination. Stringent complete response (sCR) required CR plus normal FLC ratio and absence of clonal cells in BM by immunohistochemistry or immunofluorescence. A very good partial response (VGPR) required, in addition to criteria for PR, serum and urine M protein detectable only on immunofixation but not on electrophoresis or $\geq$ 90% reduction in serum M protein and 24-hour urine M protein $<$ 100 mg/24 hours. In patients in whom the only measurable disease was by serum FLC levels, CR required a normal FLC ratio of 0.26-1.65 in addition to CR criteria. VGPR in such patients was defined as a $>$ 90% decrease in the difference between involved and uninvolved FLC levels. All response categories (CR, sCR, VGPR, and PR) require 2 consecutive assessments made at any time before the institution of any new therapy.

Disease progression required any one of the following criteria: (1) increase in serum monoclonal protein by 25% or higher above the lowest response level and an absolute increase of $>$ 5 g/L, (2) increase in urine monoclonal protein by 25% above the lowest remission value and an absolute increase in excretion by 200 mg/24 hours or greater, (3) increase in size of soft-tissue plasmacytoma by $>$ 50% or appearance of a new plasmacytoma, (4) definite appearance of new bone lesions or increase in the size of existing bone lesions by $>$ 50%, or (5) unexplained hypercalcemia $>$ 2.875mM ($>$ 11.5 g/dL).

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3, was used to grade adverse events as well as to assign perceived attribution to the study treatment regimen.

We were interested in specifically looking at responses among high-risk patients. High risk was defined, according published criteria[9] as cytogenetic studies (hypodiploidy or karyotypic deletion of chromosome 13), FISH (presence of translocations t(4;14) or t(14;16) or deletion 17p), or plasma cell labeling index (PCLI) $\geq$ 3%.

Statistical design and analysis

The primary end point for both cohorts was the proportion of confirmed responses (CR, VGPR, or PR). Both cohorts used a one-stage design with an interim analysis based on a Simon design. The 2-mg cohort tested that the true confirmed response rate was at most 45% versus the alternative that it was at least 65%, with a type 1 error of 10% and power of 85%. This cohort would be declared ineffective if a maximum of 18 confirmed responders were observed in the first 33 evaluable patients. An interim analysis was performed after the first 19 patients; if at most 8 confirmed responders were observed, the cohort would be considered ineffective. (accrual did not halt while waiting for interim analysis.) The 4-mg cohort tested that the true confirmed response rate was at most 25% versus the alternative that it was at least 45%, with a type 1 error of 10% and power of 88%. This cohort would be declared ineffective if a maximum of 11 confirmed responders were observed in the first 33 evaluable patients. An interim analysis was performed after the first 17 patients; if at most 3 confirmed responders were observed, the cohort would be considered ineffective (accrual did not halt while waiting for interim analysis). Secondary end points included overall survival (OS), progression-free survival (PFS), duration of response (DOR), and adverse event (AE) profile.

All analyses are based on an intent-to-treat principle. Exact binomial confidence intervals are constructed for the primary end point of confirmed response. The distributions of (1) OS time (time from study entry to death), (2) PFS time (time from study entry to earlier of disease progression or death), and (3) DOR (time from first documentation of response until disease progression or death), are estimated using the method of Kaplan-Meier. Simple descriptive statistics are used to summarize the AE profile and baseline characteristics.

Results

Patient population

Overall, 35 patients were accrued to the study from May 2009 to November 2009 and treated with a pomalidomide dose of 2 mg daily. An additional 35 patients were accrued from November 2009 to April 2010 and treated with a pomalidomide dose of 4 mg daily. All patients were evaluable. Patient characteristics and previous therapies at study entry are presented in Tables 1 and 2. The median number of prior regimens in each cohort was 6. All patients had previous bortezomib and lenalidomide therapy and were refractory to these agents. Baseline peripheral neuropathy was present in 29 (83%) and 24 (68%) 2 mg and 4 mg patients, respectively. The median time from diagnosis to enrollment on study was 57 months (2-mg cohort) and 72 months (4-mg cohort). Fifteen (56%) 2-mg patients and 21 (60%) 4-mg patients were classified as high risk using standard criteria (Table 1).[9]

Follow-up

The median number of cycles administered was 6 (range 1-17) for the 2-mg cohort and 3 (range 1-12) for the 4-mg cohort. Five patients in the 2-mg cohort and 4 patients in the 4-mg cohort continued to receive treatment. The major cause for stopping study

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Table 1. Baseline characteristics

	2 mg (N = 35)	4 mg (N = 35)
Median age, y (range)	62.0 (39.0-77.0)	61.0 (45.0-77.0)
Sex		
Female	8 (22.9%)	14 (40%)
Male	27 (77.1%)	21 (60%)
ECOG performance score		
0	13 (37.1%)	13 (37.1%)
1	18 (51.4%)	18 (51.4%)
2	4 (11.4%)	4 (11.4%)
Median time from diagnosis to on study, mo (range)	57.0 (11.7-248.5)	71.6 (13.3-206.3)
Cytogenetics result		
Normal	15 (44.1%)	12 (36.4%)
Abnormal	13 (38.2%)	17 (51.5%)
Not done	6 (17.6%)	4 (12.1%)
FISH		
Normal	0	1 (3.1%)
Abnormal	25 (73.5%)	26 (81.3%)
Not done	9 (26.5%)	5 (15.6%)
FISH results*		
13q−	3 (9%)	4 (13%)
Del 17, 17p−	5 (15%)	7 (23%)
t(11,14)	7 (21%)	6 (19%)
t(4;14)	3 (9%)	6 (19%)
t(14;16)	0 (0%)	2 (6%)
Other	20 (59%)	21 (68%)
High risk	15 (55.6%)	21 (60%)
ISS stage at diagnosis		
1	6 (17.1%)	10 (28.6%)
2	18 (51.4%)	17 (48.6%)
3	11 (31.4%)	8 (22.9%)
Neuropathy at baseline		
Grade 0	6 (17%)	11 (32%)
Grade 1	24 (69%)	19 (54%)
Grade 2	5 (14%)	5 (14%)
ANC, K/μL	2.2 (1.1-8.7)	2.5 (1.1-6.9)
PLT, K/μL	106.0 (77.0-279.0)	134.0 (70.0-9200.0)
HGB, g/dL	10.0 (8.2-14.4)	10.6 (7.6-14.2)
WBC, K/μL	3.8 (1.7-10.6)	3.9 (1.8-8.8)
Creatinine, mg/dL	1.0 (0.8-2.2)	1.0 (0.6-2.0)
β2 microglobulin, μg/mL	4.0 (1.9-9.6)	3.5 (2.2-13.4)
CRP, mg/dL	3.3 (0.2-335.3)	6.3 (0.6-53.1)
BM labeling, %	2.6 (0.0-10.2)	1.8 (0.0-12.0)

ECOG indicates Eastern Cooperative Oncology Group; ISS, international staging system; ANC, absolute neutrophil count; PLT, platelet; HGB, hemoglobulin; WBC, white blood count; and CRP, c-reactive protein.

*FISH probes and locus for interphase cfg FISH: 3cen (D3Z1), 7cen (D7Z1), 9cen (D9Z1), 15cen (D15Z4), 11q13 (CCND1-XT), 14q32 (IGH-XT), 13q14 (RB1), 13q34 (LAMP1), 14q32 (5′IGH,3′IGH), 17p13.1 (p53), 17cen (D17Z1).

drug was disease progression (25-2-mg and 21-4-mg patients). Four (2-2 mg/2-4 mg) patients withdrew because of physician or patient discretion. Four (2-2 mg/2-4 mg) patients have died, all because of disease progression. Four (1-2 mg/3-4 mg) patients withdrew because of adverse events. The median follow-up on the alive patients is 9.7 months (range: 1-18) in the 2-mg cohort and 6.6 months (range: 1-11) in the 4-mg cohort (Table 3). In the 2-mg cohort, 11 (31%) patients had dose reductions while in the 4-mg cohort, 12 (35%) patients dose reductions because of toxicity, primarily neutropenia.

Efficacy

Seven of the first 19 evaluable patients on the 2-mg cohort achieved a confirmed response; thus the trial did not meet the interim analysis efficacy rule. Per study design, accrual did not halt while

Table 2. Previous therapies

	2 mg (N = 35)	4 mg (N = 35)
No. of prior chemotherapies		
2	0 (0%)	2 (5.7%)
3	3 (8.6%)	6 (17.1%)
4	4 (11.4%)	2 (5.7%)
5	10 (28.6%)	4 (11.4%)
6	4 (11.4%)	7 (20%)
7	10 (28.6%)	6 (17.1%)
8	3 (8.6%)	4 (11.4%)
9	1 (2.9%)	3 (8.6%)
11	0 (0%)	1 (2.9%)
Type of prior regimens		
Lenalidomide	35 (100%)	35 (100%)
Bortezomib	35 (100%)	35 (100%)
Thalidomide	22 (63%)	20 (57%)
Transplantation	27 (77%)	28 (80%)
Autologous	25	28
Allogeneic	2	0

data for interim analysis matured. Nine (27%; 95% confidence interval [CI]: 13-45) of the first 33 evaluable patients on the 4-mg cohort achieved a confirmed response (≥ PR), which did not meet the efficacy rule for study design. Confirmed responses (≥ MR) in the 2-mg cohort consisted of VGPR in 5 (14%), PR in 4 (11%), MR in 8 (23%) for an overall response rate of 49%. In the 4-mg cohort, confirmed responses (≥ MR) consisted of CR in 1 (3%), VGPR in 3 (9%), PR in 6 (17%), MR in 5 (14%) for an overall response rate of 43%. Stable disease was the best response in 12 (2-mg cohort) and 11 (4-mg cohort) patients. The median time to response was 1 month (range: 0.8-4) for the 2-mg cohort and 2 months (range: 0.9-7.2) for the 4-mg cohort. Sixteen patients in the 2-mg cohort increased the dose of pomalidomide from 2 mg/d to 4 mg/d. Among these 16, 2 patients improved from stable disease to MR after increasing pomalidomide. Between the 2 cohorts, 36 of 62 patients were considered high risk. Cytogenetics and FISH were not available in the other 8 patients. Responses were seen in 13 of these 36 (21%) and consisted of VGPR (5), PR (4), and MR (4).

The median duration of response for the 9 responding patients (≥ PR) in the 2-mg cohort has not been reached (median follow-up: 14 months, range: 8-18); duration of response is 3.9 months

Table 3. Follow-up

	2 mg (N = 35)	4 mg (N = 35)
Progression status		
No progression	9 (25.7%)	10 (28.6%)
Progression	26 (74.3%)	25 (71.4%)
Follow-up status		
Alive	25 (71.4%)	24 (68.6%)
Dead	10 (28.6%)	11 (31.4%)
Median follow-up, alive patients, mo (range)	9.7 (1.0-17.7)	6.6 (1.2-11.3)
Median no. of cycles administered per patient (range)	6.0 (1.0-17.0)	3.0 (1.0-12.0)
Currently receiving treatment	5 (14%)	4 (11%)
Reason for ending treatment		
Refused further treatment	1 (3.3%)	1 (3.2%)
Adverse event	1 (3.3%)	3 (9.7%)
Disease progression	25 (83.3%)	21 (67.7%)
Alternate treatment	0 (0%)	2 (6.5%)
Other medical problems	0 (0%)	2 (6.5%)
Died on study	2 (6.7%)	2 (6.5%)
Other	1 (3.3%)	0 (0%)

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Table 4. Patient outcomes

	2 mg (n = 35)	4 mg (n = 35)
Confirmed response rate	26% (95% CI: 12-43)	28% (95% CI: 14-46)
No. of responders	9	10
CR	0	1
VGPR	5	3
PR	4	6
MR	8	5
SD	12	11
PD	3	8
NE	3	1
Median time to response	1 mo (range: 0.8-3.9)	1.7 mo (range: 0.9-7.2)
Overall survival*	NA	NA
Event free at 6 mo, %	78% (95% CI: 65-94)	67% (95% CI: 52-86)
Progression-free survival*	6.5 mo (95% CI: 3.9-8.9)	3.2 mo (95% CI: 1.9-8.6)
Event free at 6 mo, %	56% (95% CI: 41-75)	34% (95% CI: 21-55)

CI indicates confidence interval; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; NE, not evaluable; and NA, not attained.

*Kaplan-Meier.

(95% CI: 1-NA; median follow-up: 6 months, range: 3-11) for the 10 responding patients in the 4-mg cohort. The median PFS was 6.5 months (95% CI: 3.9-8.9) in the 2-mg cohort and 3.2 months (95% CI: 1.9-8.6) in the 4-mg cohort. The median OS time has not yet been reached in either group. Overall survival at 6 months is 78% (95% CI: 65-94) in the 2-mg cohort and 67% (95% CI: 52-86) in the 4-mg cohort. Progression-free survival at 6 months is 56% (95% CI: 41-75; 2-mg cohort) and 34% (95% CI: 21-55; 4-mg cohort). Patient outcomes are summarized in Table 4.

Adverse events

Treatment was well tolerated. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity regardless of attribution occurred in 83% (2-mg cohort) and 80% (4-mg cohort) and at least possibly attributed to the regimen occurred in 71% (2-mg cohort) and 74% (4-mg cohort). Grade 3 or 4 neutropenia (regardless of attribution) was seen in 51% (2-mg cohort) and 66% (4-mg cohort). Grade 3 or 4 nonhematologic toxicity regardless of attribution occurred in 69% (2-mg cohort) and 54% (4-mg cohort) and at least possibly attributed to the regimen was seen in 26% (2-mg cohort) and 26% (4-mg cohort). The most common nonhematologic toxicity was fatigue (2-mg cohort: 88%; 4-mg cohort: 91%) with grade 3/4 fatigue occurring in 9% of patients in both cohorts. Grade 3 pneumonia was reported in 11 (31%) patients in the 2-mg cohort; however, only 3 events were considered related to treatment. Pneumonia was reported in only 2 patients (grade 2 and 3) in the 4-mg cohort. Adverse events leading to study withdrawal consisted of rash (1 patient, 2-mg cohort), elevated bilirubin (1 patient, 4-mg cohort), neuropathy (1 patient, 4-mg cohort) and unspecified (1 patient, 4-mg cohort). Among the 2-mg cohort, 28 patients (80%) experienced neuropathy during treatment (18 grade 1; 10 grade 2). Six patients had worsening grade during treatment and 7 patients had neuropathy considered related to treatment. Among the 4-mg cohort, 31 (89%) patients experienced neuropathy during treatment (24 grade 1; 6 grade 2; 1 grade3). Ten had worsening grade during treatment and 11 patients had neuropathy considered related to treatment. Patients received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Thromboprophylaxis consisted of aspirin in 68% of cycles among the 2-mg cohort and in 65% of cycles among the 4-mg cohort. For the majority of the remaining cycles, patients received full dose anticoagulation with either warfarin or heparin. Deep vein thrombosis occurred in 2 patients (6%; 2-mg cohort) and 1 patient (3%; 4-mg cohort). Adverse events are outlined in Table 5.

Discussion

We previously reported that pomalidomide and low-dose dexamethasone (Pom/dex) is highly active in relapsed MM, with an overall response rate (PR or better) of 63%.[5] Next, to establish lack of cross-resistance with lenalidomide, we treated a cohort of patients with lenalidomide refractory disease.[6] Among 34 patients enrolled, responses of ≥ PR were seen in 31% of patients. The median time to response was 2 months and response duration was 9.1 months. Despite these promising results, important questions remained on the activity of this combination in patients with dual-refractory myeloma (resistant to both bortezomib and lenalidomide) and whether the results can be further improved by increasing the starting dose to 4 mg. In this study, we have addressed these issues through 2 sequential phase 2 trials. Our results show that the pomalidomide plus low-dose dexamethasone combination is significantly active in dual-refractory myeloma at both dosing levels, but we did not observe any advantage with the higher dose.

Our results are important because patients with myeloma that is refractory to both bortezomib and thalidomide or lenalidomide have a poor prognosis with median survival of 9 months and event-free survival of 5 months.[10] Pomalidomide plus low-dose dexamethasone offers significant hope to these patients. Our results are supported by those from the MM-002 phase 1/2 study which included patients who had previously been treated with both bortezomib and lenalidomide and were refractory to their most recent regimen. Thirty-eight patients were enrolled in the phase 1 portion of the MM-002 trial, and a partial response or better was seen in 25%.[7] The phase 2 portion of MM-002 randomized patients to receive pomalidomide alone or with dexamethasone, and provided additional supporting evidence; a total of 221 patients were enrolled and data regarding efficacy have been reported for the first 120 patients. The pomalidomide regimen was: 4 mg/d on days1-21 of each 28-day cycle. Responses of PR or better were seen in 25%.[7] In this setting, pomalidomide, with or without dexamethasone, showed promising activity and manageable toxicity in patients who had received multiple previous rounds of therapy, including both bortezomib and lenalidomide.

Our study does not show an improvement in efficacy associated with a higher starting dose. However, we studied only the day 1-28 dosing schedule. Recently, the French Intergroup reported the

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Table 5. Maximum severity of adverse events (regardless of attribution)

	2-mg cohort, %				4-mg cohort, %			
Body system/toxicity*	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Hematology								
Anemia	26	49	26	0	37	37	23	3
Leukopenia	11	31	31	9	9	23	54	6
Lymphocyte count decreased	0	3	26	6	0	6	34	3
Neutrophil count decreased	11	23	40	11	6	20	34	31
Platelet count decreased	34	23	29	3	40	14	14	17
Infection/febrile neutropenia								
Febrile neutropenia	0	0	0	0	0	0	11	0
Pneumonia	0	0	31	0	0	3	3	0
Upper respiratory infection	0	0	6	0	0	0	0	0
Metabolic/laboratory								
Hyperglycemia	0	3	9	0	0	6	3	0
Hypercalcemia	0	0	3	3	0	0	0	3
Musculoskeletal								
Fracture	0	0	6	0	0	0	6	0
Neurology								
Agitation	0	6	3	0	0	0	0	0
Anxiety	0	6	0	0	0	3	0	0
Confusion	0	3	3	0	0	0	0	0
Dizziness	0	6	0	0	0	0	0	0
Depression	0	3	0	0	0	9	0	0
Insomnia	0	6	6	0	0	3	0	0
Peripheral sensory neuropathy	51	29	0	0	69	17	3	0
Tremor	0	6	0	0	0	0	3	0
Pain								
Back pain	0	0	3	0	0	0	9	0
Pulmonary								
Dyspnea	0	3	3	0	0	3	3	0
Renal/genitourinary								
Renal failure	0	0	11	0	0	0	0	0
Cardiovascular								
Atrial fibrillation	0	3	9	0	0	0	0	0
Thrombosis	0	3	3	0	0	0	3	0
Dermatology/skin								
Rash	0	6	0	0	0	0	0	0
Constitutional symptoms								
Fatigue	11	69	9	0	31	51	9	0
Sweating	0	0	0	0	0	6	0	0
Gastrointestinal								
Anorexia	26	3	0	0	26	9	0	0
Diarrhea	26	6	0	0	14	9	0	0
Dyspepsia	0	0	0	0	0	6	0	0
Nausea	23	9	0	0	11	6	0	0
Vomiting	20	0	0	0	9	3	0	0

*Common Terminology Criteria for Adverse Events Version 3.0.

IFM 2009-02 pomalidomide study which included myeloma patients who were symptomatic and progressing following at least 2 cycles of lenalidomide and 2 cycles of bortezomib (either separately or in combination) addressed the issue of dosing schedule.[8] Pomalidomide was given orally either at 4 mg/d on days 1-21 of each 28-day (arm A) or continuously on days 1-28 of each 28-day cycle (arm B). Dexamethasone was given orally at 40 mg daily on days 1, 8, 15, and 22 of each cycle. Ninety-two were enrolled. Among 84 evaluable patients, responses of PR or better were seen in 42% (arm A) and 39% (arm B). Although our trials were sequential, not randomized, results reported here cannot confirm an advantage in starting with a more intense dosing schedule of pomalidomide. Response rates are similar with slightly higher toxicity in the group that received pomalidomide 4 mg daily.

As new drugs and regimens become available for myeloma, it is critical to evaluate response rates and toxicity in the context of how heavily pretreated and refractory to treatment the patient population is. Not surprising is the observation that the best response rates are seen in the trials with the fewest number of prior regimens (Table 6). Myelosuppression in both cohorts reported here is more pronounced than what has been reported in previous pomalidomide trials. The rate of grade 3 or 4 neutropenia was 51% in the 2-mg cohort and 66% in the 4-mg cohort. This compares to 32% in a population with 1-3 prior regimens and 26% in a lenalidomide refractory group. The higher rate in the current trials is most likely because of the refractoriness of the patient population. The median number of prior regimens is 6 with 80% and 77% having 4 or more prior regimens in the 2-mg and 4-mg cohorts, respectively. The etiology of the myelosuppression is multifactorial, reflecting a combination of poor marrow reserve, the aggressiveness of the underlying myeloma, as well as the toxicity of the regimen. A significant number of patients developed pneumonia while on

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Table 6. Response rates with Pom/Dex according to number of prior regimens

	Median no. of prior regimens	Regimen	N	Schema	Doses, mg	≥ PR, %
Lacy[5]	2	Pom/Dex	60	28/28	2	63
Leleu[8]	4	Pom/Dex	43	21/28	4	42
	4		41	28/28	4	39
Lacy[6]*	4	Pom/Dex	34	28/28	2	32
Richardson[7]	5	Pom +/−	120	21/28	4	25
Phase 2		Dex				
Richardson[7]	6	Pom +/−	38	21/28	4	25
Phase 1		Dex			MTD	
Current study†	6	Pom/Dex	35	28/28	2	26
	6		35		4	28

Pom/Dex indicates pomalidomide, 2 mg daily, with weekly dexamethasone; PR, partial response; and MTD, maximal tolerated dose.
*Lenalidomide refractory.
†Lenalidomide and bortezomib refractory.

study. However, only a minority of these episodes were attributed to study drug by the treating physicians. The difference in pneumonia rates between the cohorts was likely because of the longer follow-up in the 2-mg cohort. Similarly, the absolute number of dose reductions was similar between the groups but the follow-up in the 2-mg cohort was longer suggesting a higher rate of dose reductions in the 4-mg cohort. The rate of neuropathy and thromboembolic disease seen in these cohorts is similar to what has been previously reported for pomalidomide in myeloma.

While the study design goals were not met for either cohort, the data presented here again confirms remarkable activity of the Pom/dex regimen. The results of this study indicate that pomalidomide will be a significant drug, covering an unmet clinical need: salvage therapy for patients with disease refractory to both lenalidomide and bortezomib. Objective responses were seen in 43%-49% of a heavily pretreated refractory population and 31% of high-risk patients, a population particularly resistant to treatment at the time of relapse. Responses were durable. The overall survival rates of 78% and 67% at 6 months are far superior to what would be expected for myeloma at this advanced stage. Although it is not clear that a dose of 4 mg for 28 continuously has any advantages over the 2-mg dose, we are exploring further whether a regimen of 4 mg for 21 of 28 days is superior to 2 mg continuously. Longer follow-up and randomized trials will be needed to answer this question.

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Authorship

Contribution: M.Q.L., S.V.R., and J.R.M. designed the trial, collected and analyzed data, and wrote the manuscript; statisticians J.B.A., K.L., and S.J.M. collected and analyzed the data, and provided critical review and edits to the manuscript; and M.Q.L., M.A.G., S.R.H., K.D.S., F.B., A.D., S.K., P.R.G., J.A.L., S.J.R., D.D., S.Z., R.F., P.L.B., V.R., A.K.S., C.R., S.V.R., and J.R.M. provided study patients, and provided critical review and edits to the manuscript.

Conflict-of-interest disclosure: M.Q.L. receives research funding from Celgene. M.A.G. receives honoraria from Celgene and Millennium, and is a member of an entity's Board of Directors or advisory committees for Millennium. A.D. receives honoraria and research funding from Celgene, and honoraria from Binding Site. S.K. is a consultant for, and receives research funding from, Celgene, Merck, and Genzyme; and receives research funding from Millennium, Novartis, and Cephalon. R.F. is a consultant for Genzyme, Medtronic, BMS, AMGEN, Otsuka, and Intellikine; receives research funding from Cylene; is a consultant for, and receives research funding from, Celgene; and receives research funding from, prognosticated on FISH probes in myeloma for, and receives patents and royalties from Onyx. P.L.B. is a consultant for Celgene, Centocor, Genentech, Amgen, and Novartis. A.K.S. receives honoraria from Celgene. The remaining authors declare no competing financial interests.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Group Art Unit: 1612
Serial No.: 12/229,074	Confirmation No.: 7450
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM 501872-999773)

PETITION FOR EXTENSION OF TIME UNDER 37 CFR § 1.136(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

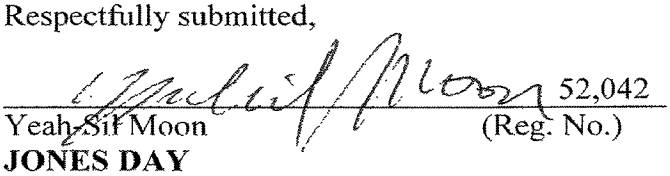
Sir:

It is respectfully requested that the time for response to the Office Action dated August 9, 2011 be extended for a period of 2 months from November 9, 2011, to and including January 9, 2012.

The fee for this extension is estimated to be $560.00. Please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: December 20, 2011



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Electronic Patent Application Fee Transmittal

Application Number:	12229074
Filing Date:	19-Aug-2008
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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